Mapping the specificity of neural deficits during sentence reading in children with dyslexia using EEG and fMRI

Thesis

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2 Summary

Background: As a prerequisite of knowledge acquisition reading is an important cultural technique in our contemporary society. During reading the meaning of words, sentences and paragraphs is decoded from abstract character strings. Despite sufficient intellectual abilities and normal schooling, children with dyslexia have difficulty in learning to read. Dyslexia is characterised by a phonological problem related to a deficit in storing and mentally manipulating speech syllables (phonemes). In dyslexia the process of reading acquisition is impaired in so far as strings of abstract characters (graphemes) are assumed to be related to inaccurately stored speech sounds. This leads to an inadequate concatenation of phonemes and graphemes and affects basic reading abilities. Hence, the reading of sentences as well as the subsequent extraction of meaning is bound to successful grapheme-phoneme conversion.

Aim: The present neuroscientific study investigates whether the impaired basic reading abilities in dyslexia also impair sentence reading and semantic processing. Further questions are related to the developmental aspects of sentence reading and semantic processing. We examined whether the impairments are specific for dyslexia or whether they are – possibly similar to younger children with less automatised reading – a consequence of reduced reading ability.

Methods: We tested dyslexic and non-impaired children from the 2nd, 3rd and 5th grade with a semantic categorisation task during silent sentence reading. The spatio-temporal aspects of brain regions and brain processes were recorded by means of event related potentials (ERP) and functional magnetic resonance imaging (fMRI). To reveal semantic processing in a fairly natural reading situation, the children read simple 4-word sentences with semantically congruent or incongruent sentence endings. To specifically consider semantic processing we computed the incongruency effect, which is the difference between incongruent and congruent sentence endings. In contrast, the brain activity for basic sentence reading and word recognition was assessed in response to entire sentences (by fMRI) and in response to all words (by EEG).

Results: In a first study we compared 5th grade children with an age-matched control group in regard to their brain response to sentence reading and semantic processing. The dyslexic children showed reduced activity in frontal and parietal brain regions during sentence reading. Furthermore, a specific semantic processing deficit for dyslexics was revealed in that a reduced and topographically changed N400 component in EEG as well as reduced activation of the inferior parietal cortex in fMRI was exhibited. To answer the question of dyslexia specificity, a 2nd study which added a further control group of 2nd and 3rd graders was conducted. The reading ability of the new group was matched to the 5th grade dyslexic group (regarding reading speed) as well as to the non -impaired 5th graders (regarding age related reading speed). The pairwise comparisons across the three groups should provide an unbiased insight into developmental factors contributing to brain activity during semantic processing and sentence reading: age, reading ability, and dyslexia. The overall results suggest that dyslexic children exhibit brain activity during semantic processing similar to that of the younger control group. Compared to the 5th grade control group both groups showed reduced activity in the inferior parietal cortex and topographical differences during the N400 onset. Furthermore, we found dyslexia specific impairments during sentence reading.

Discussion: The results of both studies revealed a semantic processing deficit in dyslexia. We found similar brain activity in dyslexics and in younger non- impaired children. Hence, the impairments are considered as non-specific for dyslexia and characterise the low level of reading ability irrespective of whether the cause is young age or whether it is a phonological deficit. We introduced the metaphor of a common endpoint preceded by two different pathways. On the one hand, due to dyslexia specific effects of basic sentence reading and word recognition, the “dyslexia pathway” terminates in a semantic processing deficit. On the other, the “pathway” for the younger control children is represented by lower reading abilities due to (developmentally conditioned) less automatised reading and leads to a (presumably preliminary) semantic processing deficit.

3 Zusammenfassung

Hintergrund: Das Lesen stellt ein elementares Werkzeug in der heutigen Bildungsgesellschaft dar. Dabei sind Wissensinhalte aus abstrakten Zeichenfolgen, den Buchstaben, zu extrahieren. Der Prozess des Lesenlernens vermittelt diesen Zusammenhang von Schrift und Bedeutungsinhalt. Bei Kindern mit Dyslexie ist dieser trotz hinreichender intellektueller Fähigkeiten mit grossen Schwierigkeiten verbunden. Gemäss heutigem Wissensstand besteht das Problem dieser Kinder in der Verarbeitung von Lauten (Phonemen). Der Prozess des Lesenlernens gestaltet sich dadurch insofern schwieriger, als dass die Umwandlung von Phonemen in eine Kette von Schriftzeichen (Grapheme) und umgekehrt nur unzureichend vermittelt werden kann. Das Lesen eines Satzes und die anschliessende Extraktion des Wissens daraus, also das inhaltlich-semantische Verständnis, ist folglich an eine erfolgreiche Umwandlung von Graphemen zu Phonemen gebunden.

Ziele: In der neurowissenschaftlichen Promotionsarbeit soll untersucht werden, inwieweit sich die beeinträchtigten grundlegenden Lesefertigkeiten bei der Dyslexie auf das Lesen einfacher Sätze und die inhaltlichen Analyse (Semantik) auswirken. Weiterhin soll geklärt werden, wie sich das Lesen von Sätzen und die semantische Verarbeitung entwickeln, und ob entsprechende Beeinträchtigungen spezifisch für die Dyslexie sind oder ob sie – ähnlich wie bei jüngeren Kindern mit noch geringerer Leseautomatisierung – eine Folge der reduzierten Leseleistung sind.

Methoden: Kinder der zweiten bis fünften Klasse mit und ohne Dyslexie wurden aufgefordert, eine sprachliche Aufgabe zur Unterscheidung zweier semantischer Kategorien zu bewältigen. Mit Hilfe ereigniskorrelierter Potentiale (EKP) und der funktionalen Magnetresonanztomographie (fMRT) sollen diejenigen Prozesse und Hirnregionen erfasst werden, die bei Fünftklasskindern mit Dyslexie während des Lesens von Sätzen und der semantischen Analyse beeinträchtigt sind. Es wurden einfache Sätze mit inhaltlich passenden (kongruenten) und unpassenden (inkongruenten) Satzendungen präsentiert. Als Mass für semantische Verarbeitung wird der Kontrast dieser beiden Kategorien erfasst. Das bedeutet, dass sich bei Betrachtung des Kontrastes die grundlegenden Lesefertigkeiten aufheben und ausschliesslich Variationen der semantischen Verarbeitung erfasst werden. Trotzdem ist es in dieser Aufgabe möglich, die Hirnantwort in Bezug auf Worte (im EEG) und in Bezug auf ganze Sätze (im fMRT) gesondert zu analysieren. In einer zweiten Studie wurde der Frage nachgegangen, ob das Lesen von Sätzen und die semantischen Beeinträchtigungen – ähnlich wie das phonologische Defizit - spezifisch für Dyslexie sind oder ob beide – möglicherweise ähnlich wie bei jüngeren Kindern mit noch geringerer Leseautomatisierung - Auswirkungen der reduzierten Leseleistung sind.

Ergebnisse: In der ersten Studie (Kapitel 7) wurden Kinder der fünften Klasse mit und ohne Dyslexie hinsichtlich ihrer allgemeinen Lesefähigkeiten sowie ihrer semantischen Fähigkeiten während des Lesens untersucht. Für die Kinder mit Dyslexie offenbarte sich eine Beeinträchtigung in der semantischen Verarbeitung die sich in einer Minderaktivierungen des inferioren Parietallappens im fMRT sowie einer reduzierten, und topographisch veränderten N400 Komponente im ERP zeigte. In der zweiten Studie (Kapitel 8) wurden die Kinder der fünften Klasse mit einer zusätzlichen Kontrollgruppe von Kindern der zweiten und dritten Klasse ohne Dyslexie verglichen. Deren Leseleistung war mit derjenigen der Fünftklasskinder mit (hinsichtlich der absoluten Lesefähigkeit) und ohne (hinsichtlich der altersnormierten Lesefähigkeit) Dyslexie vergleichbar. Durch die gemeinsame Betrachtung aller drei Probandengruppen sind Aussagen über unabhängige Einflüsse hinsichtlich des Alters, der Lesefähigkeit sowie der Dyslexiespezifität möglich. Es zeigte sich hinsichtlich der semantischen Verarbeitung, dass sich die jüngere Kontrollgruppe und die Kinder mit Dyslexie in ihrer Hirnantwort ähneln. Im Vergleich zur älteren Kotrollgruppe weisen sie eine Minderaktivität des inferioren Parietallappens, eine verzögerte N400 Komponente sowie topographische Unterschiede im Bereich des Beginns der N400 auf. Des Weiteren zeigten sich bei Kindern mit Dyslexie Beeinträchtigungen beim Lesen von Sätzen in Bezug zu beiden Kontrollgruppen.

Diskussion: In beiden Studien konnte anhand der inferior parietalen Minderaktivität und der N400 Veränderungen eine Beeinträchtigung der semantischen Verarbeitung bei Kindern mit Dyslexie nachgewiesen werden. Aufgrund der Ähnlichkeit der Hirnantwort der Kinder mit Dyslexie mit derjenigen der jüngeren Kontrollgruppe scheint dies kein dyslexiespezifischer Effekt zu sein. Verschiedenursächliche Einschränkungen der Lesefähigkeit zeitigen demnach gleiche Wirkung. Als Metapher kann hier das Bild zweier Pfade mit gemeinsamem Endpunkt dienen. Im Falle der Kinder mit Dyslexie ist es das phonologische Defizit und bei der jüngeren Kontrollgruppe bedingt die geringere Anzahl von Schuljahren die gefundenen (vermutlich vorläufigen) Defizite in der Lesefähigkeit und somit auch der semantischen Verarbeitung.

4 Introduction

Because the acquisition of knowledge is mainly bound to consulting a book, a manual, a text book or an internet encyclopaedia, one of the most important cultural techniques in modern life is reading. Our entire educational system is based on this principle. Whereas in the beginning of reading acquisition several steps have to be learned, highly proficient readers use a more direct way to assess the meaning of a word. Initially, reading for meaning requires several steps of processing, including feature extraction, word recognition, grapheme- phoneme conversion, the content analysis of the single word and finally the integration of that single word into the more global context. While children with dyslexia are hampered in their reading abilities, it is not fully understood whether this problem develops progressively to a problem of the processing of meaning.

Within a multimodal neuroscientific approach the present PhD thesis specifically considers the impaired semantic processing during reading of printed sentences in dyslexia - independently of basic word recognition. Furthermore, by comparing dyslexic children with a younger non-impaired control group matched for reading ability and with an age matched non impaired control group we are able to disentangle the specific aspects of age, reading ability and dyslexia deviance with respect to semantic processing as well as basic sentence reading and word recognition.

5 Dyslexia

5.1 Definition (ICD) R48.0

According to the World Health Organisation (WHO; International Classification of diseases, ICD-10) developmental dyslexia is considered to be an impairment of reading acquisition characterised by slow and inaccurate reading independent of any sensory problem, insufficient intellectual abilities or inadequate schooling (Dilling et al., 1991). It has been estimated that about 5% of the population is affected (Schulte-Körne et al., 2001). Having a genetic contribution (Schumacher et al., 2007), dyslexia is persistent over time and can continue into adolescence even after enormous effort (Bruck, 1992; Shaywitz et al., 1999). In addition, environmental factors such as the orthographic consistency of the language system can also contribute to the prevalence of dyslexia (Landerl et al., 1997a; Paulesu et al., 2000). The entanglement between genetic contributions of dyslexia and environmental factors as well as their relation to functional brain process is still unknown.

5.2 The phonological core problem of dyslexia and its relation to semantic processing

There are several conflicting theories associating dyslexia with sensory (magnocellular theory, auditory impairment) or sensorimotor (balance, motor control) deficits. Recent research has shown, however, that dyslexia can be best explained by a phonological deficit. The phonological deficit theory postulates an impaired representation, storage and/or retrieval of speech sounds for dyslexics (Ramus, 2001; Ramus, 2003). Accordingly, during reading acquisition, this inappropriate processing of phonemes leads to hampered learning of the phoneme-grapheme conversion. Grapheme-phoneme conversion refers to the correspondence between letters and speech sounds.

The recognition of dyslexia may also depend on the regularity of the writing system and is hence variable across languages. Despite the same underlying phonological processing deficits, reading acquisition is facilitated for languages containing a consistent and shallow orthography (e.g. Italian and German). In contrast, for languages with inconsistent and deep orthography (e.g. English and French) the impairments dyslexic children suffer from are much greater and lead to increased impairment in reading performance (Landerl et al., 1997a; Paulesu et al., 2000). As impaired and non-impaired children are equally concerned, the relative impairments do not differ across these languages (Landerl et al., 1997a; Paulesu et al., 2001). These findings lead to the assumption of a common neurocognitive basis for dyslexia at least for western languages.

A major problem in the diagnosis of dyslexia is that it can be assessed only after reading acquisition. Hence, there are a few studies which have aimed to delineate possible precursors of dyslexia. While dyslexia is related to a deficit of speech sound processing, these (by definition) longitudinal studies have mainly focussed on language factors. A recent study by Maurer et al. (in preparation) presented tones and phonemes in an ERP mismatch negativity design (MMN) as well as behavioural measures to predict future struggling readers. They found that the lateralisation of the MMN score assessed in kindergarten age contributes significantly to the reading outcome in the 5th grade. A further study applying a follow-up testing of reading achievement in kindergarten predicted the reading outcome in the 2nd grade. They identified four language related variables (letter identification, sentence imitation, phonological awareness, rapid naming) and the mother's education as relevant for future reading abilities (Catts et al., 2001). These authors also found an increased risk for developing dyslexia in children with parents who are also affected. Militating for a genetic contribution, the ERP study on newborn infants in response to speech and non-speech syllables of (Molfese, 2000) differentiates poor readers, dyslexic and non-affected children at the age of 8 with an accuracy of 92%. These initial difficulties in reading acquisition may also accrue to a deficit of knowledge acquisition, as indicated by a semantic coding deficit occurring only in 6th grade dyslexics but not in 2nd and 3rd grade dyslexics (Vellutino et al., 1995).

By using a large toolbox of methods, neuroimaging research can reveal the contribution of those mechanisms in dyslexia that underlie the deviant processing of spoken language and print as well as of possible compensatory processes.

5.3 Multimodal assessment of semantic processing in dyslexia

The present work applied a new multimodal approach that is particularly suited to assessing semantic processing during sentence reading in dyslexia. To adequately describe overt behaviour as well as underlying mechanisms, a multimodal approach is mandatory. The use of EEG and fMRI and their relation to individual reading abilities allows the characterisation of spatio-temporal aspects of brain activity during semantic processing. The high resolution recording in the temporal domain with EEG provides an assessment of fast brain processes within a range of milliseconds. Complementarily, fMRI, with its high spatial resolution, localises neuronal activity in the brain. Dyslexia research that includes behavioural research, neurophysiological as well as fMRI studies has already revealed brain processes functioning deviantly in dyslexics in relation to their age norm. Until now no investigation has described the spatio-temporal aspects of brain activity specific to sentence reading and semantic processing in dyslexia by combining behavioural and two neuroimaging methods within one study.

5.4 Semantic impairments in dyslexia (age-matched comparisons)

5.4.1 Behavioural research

Despite several years of behavioural research the published findings focussing on reaction times and error rates in semantic tasks are fairly inconsistent. While most behavioural studies have demonstrated inefficient semantic processing in poor readers (Chabot et al., 1983; Howell and Manis, 1986; Murphy et al., 1988; Stanovich et al., 1988; Vellutino et al., 1995) other studies have failed to find any deficiencies (Jorm, 1979; Waller, 1976; Waterman and Lewandowski, 1994). Further studies have shown that - if possible - dyslexic children rely more on the semantic processing system (context, semantic coding) than normally reading children, compensating to some extent for poor phonological decoding skills (Nation and Snowling, 1998; Vellutino et al., 1995). Nevertheless, whereas behavioural studies are able to show only overt behaviour the underlying deviant processes and compensatory mechanisms on the neuronal level remained unknown.

5.4.2 Neurophysiological studies

Neurophysiological studies on semantic processing mainly apply a visual N400 ERP paradigm. Due to high resolution recording in the temporal domain, these methods are able to follow the time course of brain processing. The N400 component is characterised by a negativity at centroparietal electrode sites and represents higher order language processing at around 400ms after stimulus presentation. Indicating semantic processing, it shows a larger negativity for unexpected (incongruent) sentence endings than for expected (congruent) sentence endings (Kutas and Hillyard, 1980). While several neurophysiological studies revealed an impaired semantic processing in dyslexics by recording a reduced or delayed N400 component (Brandeis et al., 1994; Helenius et al., 1993) other researchers (Robichon et al. (2002); Neville et al. (1993)) found an even larger N400 for dyslexics than for controls. Another study by Sabisch and colleagues (2007) did not find a dyslexia effect in an auditory N400 paradigm.

5.4.3 fMRI studies

fMRI studies localised the deficit of semantic processing in dyslexia to posterior brain regions. These studies mainly used tasks with semantic performance (e.g. semantic categorisation) but without an explicit semantic analysis. (Shaywitz et al.,

2002) found a correlation between reading speed and brain activation in the occipitotemporal region. Kronbichler et al. (2006), studying adolescents, found reduced activity for dyslexics in middle temporal and supramarginal regions. Furthermore, Meyler and colleagues (2007) examined dyslexic and non impaired 3rd and 5th graders and found reduced activity in middle temporal and (right hemispheric) inferior parietal regions in dyslexic children. In a specific semantic task Booth et al. (2007) correlated the semantic association strength of words with the brain activation for these words and found a weaker correlation for dyslexic children in inferior frontal, middle temporal and inferior parietal regions. It is unclear, however, whether the study results cited above are confounded by impaired basic reading mechanisms (Shaywitz et al., 2002) or are restricted to single word processing (Booth et al., 2007). A combined approach with an explicitly semantic task embedded within the sentence context would clarify this vagueness. Furthermore, while these studies on dyslexia compared a target group consisting of impaired readers with a control group of non impaired readers usually matched for nonverbal intelligence, age and gender, a major disadvantage of these neuroimaging studies on dyslexia is that unspecific effects of dyslexia depending on limited reading experience can not excluded (Backman et al., 1984).

5.5 A new approach in neuroimaging: the reading level matched design

Due to these limitations a potential drawback of the previous studies is that one cannot solely attribute group differences to the deliberate task design (Bradley and Bryant, 1978). Hence, without the ability to distinguish cause from effect it remains open whether the results are specific for dyslexia and whether they are confounded by differences in preceding stages of language processing (e.g. feature extraction) and task difficulty as indicated by reduced reading speed (Backman et al., 1984; Bradley and Bryant, 1978). Thus, the enhanced task requirements for dyslexic children, especially in demanding and/or complex language tasks may lead to difficulties during earlier steps of language processing and may affect the processing of subsequent stages. For example, for tasks using a very fast presentation rate the results may rely more on basic word recognition mechanisms rather than on the actually intended subsequent stages of language processing (e.g. semantic processing). This is especially true for reading impaired children performing worse in tasks assessing basic sentence reading and word recognition mechanisms

(Kronbichler, Maurer, (Price and Friston, 1999). In dyslexia research, this problem has been addressed by comparing dyslexic children with younger children, matched for reading ability (for non-imaging research see (Bradley and Bryant, 1978; Goswami et al., 2002; Snowling et al., 2000; Wimmer, 1996); for neuroimaging: (Hoeft et al., 2006; Hoeft et al., 2007). Within this reading level design, the differences obtained are not related to reading performance (Backman et al., 1984). Just as with the age-matched contrasts, differences in reading level matched groups can be reasonably described as effects of dyslexia.

In these cases, confounded by age, findings of impaired processing in dyslexics or attributed compensatory strategies allow only tenuous interpretations. To detect unconfounded effects of dyslexia further steps are mandatory. First, an age matched comparison with a group of dyslexics and a control group is required. This is done by most neuroimaging studies (see 2.4). A second necessary comparison is that of dyslexic children with reading level matched younger children. This comparison may show similar effects to those detected by the same-age contrast and would point to a dyslexia specific cause. On the other hand, no difference between these groups and additionally the same kind of difference between an older and a younger control group would suggest (something like a) developmental delay. Similar to the age-matched contrast, possible compensatory strategies of dyslexics indicated by higher activations in certain brain regions or larger ERP components can also be assessed (Eden and Zeffiro, 1998; Nation and Snowling, 1998; Shaywitz et al., 2002). Third, the comparison of both control groups (the younger vs. the older) would reveal effects that develop with age and increasing abilities. To isolate age related from performance related effects, comparisons with the dyslexic group can– with some reservations - be taken into consideration.

5.6 Conclusion/ Hypotheses

Thus, the phonological impairment is considered as the core deficit of dyslexia which may subsequently interfere with the process of learning to read. This deficit should be evident during basic word recognition processes right from the start. However, it is unclear whether subsequent stages of language development or of general education, such as improvements in language expression and semantics, are hampered. Continuous progress in reading and writing may lead to a mutual improvement of basic word recognition and higher order language processing such as semantics. Hence, effortless reading may lead to an ease in dealing with knowledge. And conversely, as a strong thirst for knowledge necessarily requires reading, that in turn may enhance reading abilities. Unfortunately, it is unclear whether the described impairments are specific for dyslexia or might be related to the degree of expertise with language and script.

Complementing behavioural and neuroimaging studies we examine semantic processing in dyslexic 5th grade children in comparison to their age matched control group (see chapter 2.3). By utilising a task approaching a rather natural reading situation we hypothesise an affected semantic processing in dyslexic 5th graders. For dyslexic children we would expect a decreased accuracy and an increased response time that have their neurobiological equivalent in a deviant semantic modulation around 400ms and in posterior brain regions.

In a second study by applying the reading-level matched design introduced in chapter 2.4 we want to extent the findings of the first study and of the previous studies on phonological processing by (Hoeft et al., 2006; Hoeft et al., 2007). By probing basic sentence reading and word recognition as well as semantic processing we investigate the effects of age, dyslexia and reading ability on brain activity. We examine whether the semantic processing deficit is specifically related to dyslexia or whether it can be explained by reduced reading speed.

6 Impaired semantic processing during sentence reading in children with dyslexia: combined fMRI and ERP evidence

6.1 Introduction

Developmental dyslexia is a specific disorder of reading acquisition with a high prevalence and a marked familial risk. There is a general approval that dyslexia is characterised by a phonological core deficit (Ramus, 2001; Ramus, 2004).

Neuroimaging studies on the neural basis of dyslexia consistently reveal reduced activation in response to words or word-like stimuli within posterior parts of the reading network in the brain of adults and older children with reading disability (Brambati et al., 2006; Brunswick et al., 1999; Rumsey et al., 1997; Shaywitz et al., 2002; Shaywitz et al., 1998; Temple et al., 2001). Reduced activation in superior temporal and inferior parietal regions has been linked to the phonological core deficit in dyslexia, while reduced activation in inferior occipitotemporal regions suggests deficits in specialised visual word processing (McCandliss et al., 2003). In addition, increased frontal activation in older dyslexic readers suggests the development of compensatory neural mechanisms (Georgiewa et al., 2002; Shaywitz et al., 1998).

Most of these neuroimaging results have focused on deviant processing of isolated word-like stimuli. While this approach has successfully identified regions associated with the phonological deficit, it may not represent a sufficiently natural reading situation, in which semantic expectations based on context can facilitate word processing (DeLong et al., 2005). It remains unclear, whether such lower-level deficits also dominate during sentence reading, and how they affect higher order language processing.

Recent studies have thus started to investigate how brain processes during sentence reading are affected by dyslexia in children (Meyler et al., 2007) and adolescents (Kronbichler et al., 2006). Increased activation in left middle temporal regions was associated with better reading in 3rd and 5th grade children (Meyler et al., 2007), and also in adolescents (Kronbichler et al., 2006). In contrast to this age-independent effect activation in the left inferior parietal cortex was associated with better reading ability, but more in 5th graders than in 3rd graders, suggesting a developmental influence (Meyler et al., 2007). Consistent with this result a similar inferior parietal region was more strongly activated in adolescent fluent readers than in dyslexics (Kronbichler et al., 2006). Moreover, whereas in the children there was no region showing more activation with lower reading ability, in adolescents left inferior frontal regions were more strongly activated in dyslexics than in controls, suggesting that frontal compensatory mechanisms in dyslexia may develop over time (Georgiewa et al., 2002; Shaywitz et al., 1998). In addition, a region of interest analysis for the inferior occipito-temporal cortex revealed reduced activation in the visual word form area in adolescent dyslexics (Kronbichler et al., 2006).

While these studies show that neural processing in more natural reading situation is also impaired in dyslexia, they do not inform us whether this neural impairment specifically reflects semantic processing, as sentence reading encompasses not only semantic processing, but also additional, more basic word recognition processes typically preceding semantic elaboration, such as visual word recognition and phonological processing.

To isolate semantic effects during sentence reading with ERPs (Brandeis et al., 1995; Kutas and Hillyard, 1980), one typically contrasts sentence endings that are incongruous (unprimed) and congruous (primed) in the sentence context. The time-sensitivity of the ERP method reveals that incongruous sentence endings are processed differently from congruous endings and elicit a response which is more negative at parietal sites and more positive at anterior temporal sites while peaking at around 400 ms ((Brandeis et al., 1995; Kutas and Hillyard, 1980). This ERP difference (i.e. incongruous minus congruous) around 400 ms is called the N400-effect (Brandeis et al., 1995).

A few ERP and MEG studies also investigated how dyslexic participants differ from controls during sentence reading. Brandeis et al. (1994) reported that 12-year-old children with dyslexia differed from controls during sentence reading especially for sentences with incongruous endings. An early segment of the N400 component differed in topography between dyslexics and controls, and was parietocentrally less negative for incorrect endings in dyslexics. Additionally, a late segment of the N400 was delayed in dyslexic children. Delayed and attenuated N400 incongruency effects were also reported in dyslexic adults in an MEG study (Helenius et al., 1999), whereas in another study with ERPs, the N400 incongruency effects were similar in adult dyslexics and controls, although the N400 itself was larger in dyslexics with slow presentation (Robichon et al., 2002). The semantic processing impairment seems to change with both development and modality, as younger children with dyslexia and language impairment tended to show even increased N400 incongruency effect during sentence reading (Neville et al., 1993).

Taken together the results of these ERP studies suggest that semantic processing during sentence reading may differ between disabled readers and controls from an early age on at around 400 ms, but they leave open which brain regions are involved.

To address these questions, children with dyslexia were asked to read sentences with congruous and incongruous endings while we recorded their brain responses with fMRI and ERP techniques and compared them to a matched control group. This allowed us to characterise spatio-temporal aspects of their neural processing deficits during sentence reading, and especially during semantic processing.

We hypothesised that semantic effects during sentence processing would affect dyslexic children differently from controls indicated by reduced differences between incongruous and congruous sentence endings in posterior brain regions and around 400 ms. Semantic processes were defined as differential processing of incongruous and congruous endings, as opposed to basic word processing common to all words.

6.2 Materials and Methods

Subjects

The 52 children (mean age 11.5 years) who participated were grouped according to their reading scores (see Table 6.1): 16 children with dyslexia, 31 control children, and 5 children falling between the categories for dyslexic and normal reading. 44 children were part of a longitudinal study (Maurer et al., 2007; Maurer et al., 2003), 8 children participated only in 5th grade.

Table 6.1: group characteristics

	Whole group (n=52) (10.8 – 12.7 years) (23 girls)		Dyslexics (n=16) (10.9 – 12.2 years) (8 girls	Controls (n=31) (10.8 – 12.7 years) (14 girls)	D vs. C
	mean ±SD	Correlation with wpm	mean ±SD	mean ±SD	t-test
Age (y)	11.5±0.37	-0.25	11.6±0.3	11.4±0.4	p > 0.12
estimated non verbal IQ	111 ±12	-0.11	111 ±12	110 ±11	p > 0.2
estimated verbal IQ	108 ± 12	0.15	106 ±14	109 ±12	p > 0.2
Correct words per minute	78±23	-	49±7	93±13	p < 0.001
All words per minute	80±22	0.99***	53±7	94±13	p < 0.001
Correct pseudowords per minute	46±14	0.85***	33±5	54±12	p < 0.001
wpm SLT	117±31	0.85***	84±16	135±25	p < 0.001

The children were screened for a history of neurological diseases or psychiatric disorders, and reported all normal or corrected-to-normal vision. Children from families with a foreign language background (i.e. both parents' first language was not (Swiss-) German) were excluded from the study.

All children participated in two counterbalanced sessions with EEG and fMRI recordings, except for 14 children (4 with dyslexia, 9 controls, 1 from the between-category) who could not participate in the MR session because of dental braces. In addition, one control child was excluded from fMRI analysis, because of excessive movement artefacts (> ±1.8mm in each direction or > ±2° in each rotation axis). In 8 children (3 with dyslexia, 3 controls, 2 from the between-category) the movement artefacts were in the acceptable range, after the experiment was run in an additional fMRI session. For the ERP data 2 children from the control group had to repeat the experiment because of technical problems. The main analyses run without these children replicated the results for the full group and are thus not reported. Children and their parents gave informed consent, and were compensated with a book voucher of 60 CHF for their participation.

Reading skills in 5th grade were assessed with a reading fluency measure, which is the core criterion to diagnose dyslexia in readers of the regular German orthography (Wimmer et al., 2000). To this end we used the "Ein-Minuten

Leseflüssigkeitstest" (Willburger and Landerl, 2008), which requires the children to read from a list as many words as possible within 1 minute without making mistakes. The resulting "correct words per minute" score was compared to the distribution in a normative group of 56 children. These additional children were recruited from 5 different school classes reflecting the origin of the children in the ERP/fMRI study (2 from neighbourhoods in Zurich with higher socio-economic background, 2 from neighbourhoods in Zurich with lower socio-economic background, 1 from a rural area outside of Zurich), and were not further selected except for foreign language background (the same criterion as in the ERP/fMRI study), and for continuous schooling in German.

The reading scores in this normative group ranged from 42 to 138 correct words per minute with a mean value of 89, a median of 90, and a standard deviation of 18. The lack of prominent skewness (-0.38, SE = 0.32) and kurtosis (0.69; SE = 0.63), allowed for simple standardization.

Children from the ERP/fMRI study were classified as dyslexic if their "correct words per minute score" was below 10% of the norms (<61.6), and as controls if their score was equal or above 20% (≥75.0). The children with intermediate scores were excluded from the dyslexic-control group comparisons but included in the correlation analyses.

The result corresponded well with the classification based on a published reading test (Landerl et al., 1997b) that most children from the longitudinal subsample had taken in 3rd grade. Accordingly, 13 (86.7%) of 15 dyslexic children in 5th grade, had been classified as dyslexic in 3rd grade, and the others as belonging to the intermediate category. No dyslexic 5th grader had been classified as a normal reader in 3rd grade. Similarly 22 (91.7%) of the 24 control children in 5th grade had been classified as normal readers, 2 as intermediate readers, but none as dyslexic in 3rd grade.

Nonverbal and verbal intelligence was assessed in 5th grade using the block design and the similarities subtest of the HAWIK-III intelligence test (Tewes et al.).

As can be seen in Table 6.1, the children with dyslexia were not only slower in word reading (the criterion for grouping), but also in pseudoword reading. In contrast the groups did not differ in their estimated IQ (neither nonverbal nor verbal), and the small age difference (<2.5 months) also missed significance.

Task

Identical sentence reading tasks with semantically congruous and incongruous endings were used with EEG and fMRI. Some adaptation of the original (Brandeis et al., 1994) was necessary to allow also presentation in fMRI. From the original pool of sentences we chose 112 simple sentences with semantically congruous (50%) or incongruous (50%) endings ("The sky is blue / fat") and added 20% null events for event-related fMRI modelling. The congruous sentences contained 48 colour word endings and 8 non colour word endings. The incongruous sentences ended with 48 non colour words and with 8 colour words. The children were asked to read the sentences silently, and to press a mouse button with the index or the middle finger of the right hand only occasionally, i.e. if the question 'Yes – No?' appeared after a sentence prompting their judgement on whether the previous sentence had been meaningful or not. While 32 sentences required an explicit judgement (28.6%; 8 from each category), 40 sentences with congruous colour endings and 40 sentences with incongruous non colour endings were not followed by a motor response and were used for the ERP and fMRI analyses.

In contrast to two earlier fMRI studies on sentence reading in dyslexia (Kronbichler et al., 2006; Meyler et al., 2007), we presented the words sequentially to allow for better modelling of the semantic priming effect to sentence endings with both event-related fMRI and ERPs. Each word in a sentence was presented in the centre of the screen for 280 ms with an SOA of 570 ms. For the sentences requiring a (delayed) response, an additional 'Yes – No?' screen was presented following the offset of the final word after 1080 ms. The sentence SOA (for all sentences) and the duration of the null events were 4700 ms. Congruous sentences, incongruous sentences and null events occurred in a pseudo randomised order for 14 min. The assignment of the response buttons to the semantic judgment was counterbalanced across subjects. Both the fMRI and the ERP session included further tasks presented in a pseudorandomised order.

fMRI recording and analysis

Whole brain functional imaging data were acquired in the Children's Hospital Zurich on a 3T (GE medical systems) scanner using T2*-sensitive ultrafast multi-slice echo planar imaging (EPI) sequences sensitive to blood oxygenation level dependent (BOLD) contrast. The task was projected using MR compatible video goggles. The entire scanning session included 3 additional tasks and lasted about 2 hours. Children took a break (or more than one if necessary) during the scanning session between the tasks.

In an event-related design we recorded 566 volumes (25 axial slices of 4.6 mm with 0.4 mm gap between slices, TR = 1499ms, TE= 40 ms, slice resolution = 3.75 mm x 3.75 mm, 64 x 64 pixel matrix, flip angle 50°). The first 5 volumes were rejected to exclude T1 saturation effects. T1-weighted structural images were acquired using a standard 3-dimensional (3D) T1-weighted gradient echo sequence (172 slices, TR = 9.34 ms, TE = 2.1 ms, flip angle = 20°, voxel size = 1 × 1 × 1) to obtain a structural 3D volume.

Particular care was taken to stabilise the children using a vacuum cushion, custom made padding and fixations. As a result, the head movements were below 2° in all rotation axes and below 50% of the voxel size in each direction for all children except for one child who was excluded. To reduce noise subjects were also provided with earplugs.

Image processing and statistical analyses were carried out using SPM5 (Wellcome Department of Cognitive Neurology, London, http://www.fil.ion.ucl.ac.uk/spm). We were using the standard preprocessing steps including slice-scan-time correction, movement correction, normalisation to the Montreal Neurological Institute (MNI) template, and smoothing with a Gaussian kernel of 9 mm.

For statistical analysis the data were high pass filtered with a cut-off of 128 s. In one event-related first level analysis we computed the sentence reading activations of any child. To model the design we used the onset of the first word of every sentence with the duration of 2.25s (1.5 scans) in fMRI statistics. The sentences which required a response were modelled separately but excluded from further statistical analysis.

In a second event-related first level analysis we focussed on the semantic incongruency effect comparing incongruous and congruous sentence endings. The first 3 words of each sentence, the null events and the response screens were all not modelled and served as an extended baseline to detect the percentage of signal change for the sentence ending. The onset of the final word in each sentence served as a single event and was convolved with the SPM5-implemented hemodynamic response function. Incongruous (n=40) and congruous (n=40) sentence endings which did not require a response were modelled separately as regressors of interest. Sentence endings which required a response were modelled separately but excluded from further statistical analysis.

For both group analysis designs we conducted the SPM5 implemented standard whole brain second level random effects analysis. We computed one-sample t-tests to reveal the entire group activations for sentence reading, the group's additional activations while processing incongruous sentence endings compared to congruous sentence endings (incongruency effect) as well as the opposite contrast between congruous and incongruous sentence endings (congruency effect).

To detect the effect of dyslexia we computed group comparisons with two sample t-tests between dyslexic and control children for sentence reading versus fixation baseline as well as for the incongruency effect.

We further used a correlation approach to investigate effects of reading skills on semantic processing (Meyler et al., 2007). The "correct word per minute" score was added as a covariate in the second level analysis using the single subject contrast images provided by the SPM5 first level analysis of individual data.

The effects of dyslexia were analysed in more details with a region of interest (ROI) analysis on unsmoothed data to explain the incongruency effects of the voxel based analysis. MarsBar software (version 0.41; (Brett et al., 2002) was used to extract the regions mean signal change in percent. The ROIs were defined by local maxima of the voxel based between-group comparisons ($p<0.001$, uncorrected). If not reported otherwise, the ROIs had a radius of 9mm, and are reported in Talairach coordinates.

We computed further ROIs based on the literature: A spherical ROI was located in the left fusiform gyrus centred at −43/ −54/ −12 (r= 5mm) corresponding to the VWFA (Cohen et al., 2000; McCandliss et al., 2003). Additional spherical ROIs were located in the left middle temporal gyrus centred at -65/ -52/ 6 (Meyler et al., 2007) and at −57/ −60/ 3 (Kronbichler et al., 2006). These regions are known to be less activated in dyslexics during sentence reading (Kronbichler et al., 2006; Meyler et al., 2007), and generally during visual word processing (McCandliss and Noble, 2003).

ERP recording and analysis

The EEG was recorded at the Department of Child and Adolescent Psychiatry, University of Zurich, using Synamps-1 (Compumedics Neuroscan, Charlotte, USA) amplifiers and an electrode cap (FMS, Munich, Germany). The children were seated in an electrically shielded, sound proof and air-conditioned room on a computer screen 1.2m away. The entire ERP session lasted about 3 hours.

The electrode montage included 65 electrodes consisting of all 10-20 system electrodes and the additional electrodes Fpz, FCz, CPz, POz, Oz, Iz, AF1/2, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5, TP7/8/9/10, P5/6, PO1/2/9/10, OI1/2 plus two electrodes below the outer canthus of each eye. The electrodes O1/2 and Fp1/2 were placed 5% more laterally for more even coverage indicated by an apostrophe in the label (e.g. O1').

The EEG was referenced to the Fz electrode, sampled at 500 Hz/channel, bandpass-filtered between 0.1 and 70 Hz and calibrated to technical zero baseline. The impedance was kept below 20 kΩ (Ferree et al., 2000).

The ERPs were processed in Vision Analyzer software (Brain Products GmbH) including downsampling to 256 Hz, digitally low pass filtering with a 30 Hz filter, correcting for horizontal and vertical eye movements using and independent component analysis (Jung et al., 2000) and transforming to the average reference (Lehmann et al., 1980). Trials with artefacts exceeding ±100 µV in any channel (2 children ±120 µV) were automatically rejected. Before averaging the remaining trials were epoched 125 ms prior and 1125 ms following the stimulus.

ERPs were computed for 3 conditions from sentences that did not require a response: all words irrespective of position in a sentence, congruous sentence endings, and incongruous sentence endings. Difference waves were computed by subtracting the congruous ERP from the incongruous ERP.

The mean number of averaged sweeps was 397 (SD: ±47, range: 276-448) for the ERP in response to all words, and 36 each for the ERPs in response to incongruous (SD: ±4, range: 26-40) and congruous endings (SD: ±4, range: 22-40). Six children (2 with dyslexia, 4 controls) had an average number of less than 30, but visual inspection of their corresponding ERPs revealed no anomalies.

Grand averages were computed from the condition including all words and from the incongruous minus congruous difference wave.

For further analyses, time windows reflecting basic visual word processing and time windows reflecting semantic processing were selected based on the data of all 52 children. Time windows reflecting basic visual word processing were selected using adaptive segmentation according to maxima and minima in Global Field Power of the grand mean of the ERP in response to all words (see (Maurer et al., 2005a; Maurer et al., 2005b; Maurer et al., 2006).

Time windows reflecting semantic processing were selected using Topographic Analysis of Variance (TANOVA) on raw ERP data (Maurer et al., 2003; Strik et al., 1998) indicating when congruent and incongruent sentence endings were processed differently ($p<0.01$).

In addition a hierarchical clustering algorithm (using the Cartool software by Denis Brunet: http://brainmapping.unige.ch/Cartool.htm) was applied to these time windows in order to test whether they could be further subdivided in microstates with constant ERP map topographies. Map clusters that correlated highly (>92%) were treated as one microstate.

An ERP mapping approach was used to analyse group differences between dyslexic children and controls. Mean microstate maps were computed at the individual level for ERPs averaged over all words (sentence reading) and for the ERP difference between incongruous and congruous endings (semantic processing). For each of the microstates we analysed group differences in map strength (t-test on GFP), and in map topography (TANOVA bootstrapping statistics). We computed TANOVA for both raw maps and normalised maps. The 3 statistical tests are complementary: t-tests on GFP reveals differences in map strength independent of topography, TANOVA on normalised maps reveals differences in topography independent of map strength, and TANOVA on raw maps reveals amplitude differences with constant topographies.

In addition we used statistical t-maps for the group comparisons in the figures to facilitate interpretation of the results.

In order to test for latency differences between dyslexic children and controls we applied a Topographic Component Recognition (TCR / (Brandeis et al., 1992; Brem et al., 2005). TCR uses a template map to search for the topographically most similar map in each individual ERP. For each microstate the mean segment in the grand mean of the 52 children was taken as template. In order to avoid a topographical match with noise time points with high GFP (i.e. low noise) were favoured by adding 5% GFP to the correlation (Brem et al., 2005; Steger et al., 2000). The latencies of the time points with the highest correlations were chosen for the group comparisons (t-tests).

To reveal brain regions which contribute to the topographic maps we computed the sources with the distributed source solutions LORETA (low resolution electromagnetic tomography, (Pascual-Marqui et al., 1994) and LAURA (local auto-regressive average model, (Grave de Peralta Menendez et al., 2001) at the GFP peaks of the grand mean of the N400b (379ms) and the late positivity (973ms). This inverse solution is based on the SMAC transform (Spinelli et al., 2000) of a realistic head model which is made of an average brain of 152 MRIs (Montreal Neurological Institute, Montreal, Canada) as implemented in the CARTOOL software (http://brainmapping.unige.ch/Cartool.htm).

6.3 Behavioural analysis

As more children participated in the EEG than in the fMRI session, behavioural data were analysed separately for EEG and fMRI sessions, and also separately for accuracy and reaction time resulting in 4 multivariate ANOVAs for repeated measures with the within subject factor "incongruency" (incongruous vs. congruous) and the between subject factor "dyslexia" (dyslexic vs. control children). The incongruous condition was composed of responses to both incongruous colour and incongruous non-colour endings, the congruous condition of responses to both congruous colour and congruous non-colour endings.

6.4 Results

6.4.1 Behavioural data

The behavioural analyses revealed that control children responded faster and were more accurate than dyslexic children in both the EEG (accuracy: $F(1,45)= 10.8$, $p<0.01$; reaction time: $F(1,45)= 9.6$, $p<0.01$, Supplemental Material, Table 6.1) and the fMRI (accuracy: $F(1,32)= 18.6$, $p<0.001$; reaction time: $F(1,32)= 11.2$, $p<0.01$) sessions. In addition, the children responded faster to congruous than incongruous endings in both sessions (EEG: $F(1,45)= 4.3$, $p<0.05$; fMRI: $F(1,32)= 5.5$, $p<0.05$), and were more accurate for incongruous than for congruous endings, although this difference reached significance only in the fMRI session ($F(1,32)= 5.5$, $p<0.05$), but not in the EEG session (F(1,45)= 2.2, p>0.1). The dyslexia factor did not interact with the incongruency factor in any of the analyses (EEG: both p>0.1; fMRI: both p>0.2).

Table 6.2. Behavioural data

	EEG				fMRI			
	congruous		incongruous		congruous		incongruous	
	Dys (n=16)	Ctrl (N=31)	Dys (n=16)	Ctrl (N=31)	Dys (n=12)	Ctrl (N=22)	Dys (n=12)	Ctrl (N=22)
Acc (%) (±SD)	85.8 (±9.4)	94.5 (±6.0)	90.3 (±8.4)	94.5 (±8.7)	82.3 (±14.6)	95.1 (±5.8)	88.3 (±9.7)	96.7 (±4.9)
RT (ms) (±SD)	1397 (±335)	1140 (±300)	1536 (±432)	1163 (±336)	1325 (±348)	982 (±225)	1402 (±336)	1071 (±324)

6.4.2 fMRI results

Sentence reading

All children. The whole group voxel-based fMRI analysis of sentence reading revealed a language network including large portions of the left frontal gyrus, the right inferior frontal gyrus, the left fusiform gyrus, the left middle occipital gyrus, the left superior parietal lobe, the left precuneus and the left middle temporal gyrus (p < 0.05, FWE corrected, Table 6.3, Figure 6.1A).

Group contrast. Dyslexic children showed less activation than normal reading control children in left hemispheric regions: the medial frontal gyrus, the superior frontal gyrus, the inferior parietal gyrus, the angular gyrus and the precuneus (2-sample t-test, p < 0.001 uncorrected, Table 6.3, Figure 6.1B). We found no activated region for the opposite contrast (2-sample t-test, p < 0.001 uncorrected).

Reading speed covariate. We also computed a voxel-based analysis with reading speed as a covariate including all 38 children which corroborated the results from the group comparison. We found an increased activation with increasing reading speed in the superior frontal gyrus, the anterior cingulate gyrus and the inferior parietal gyrus (Supplemental Material, Fig. 6.1A; p < 0.001 uncorr.; Supplemental Material, Table 6.2) . We did not find any region negatively correlated with reading skills.

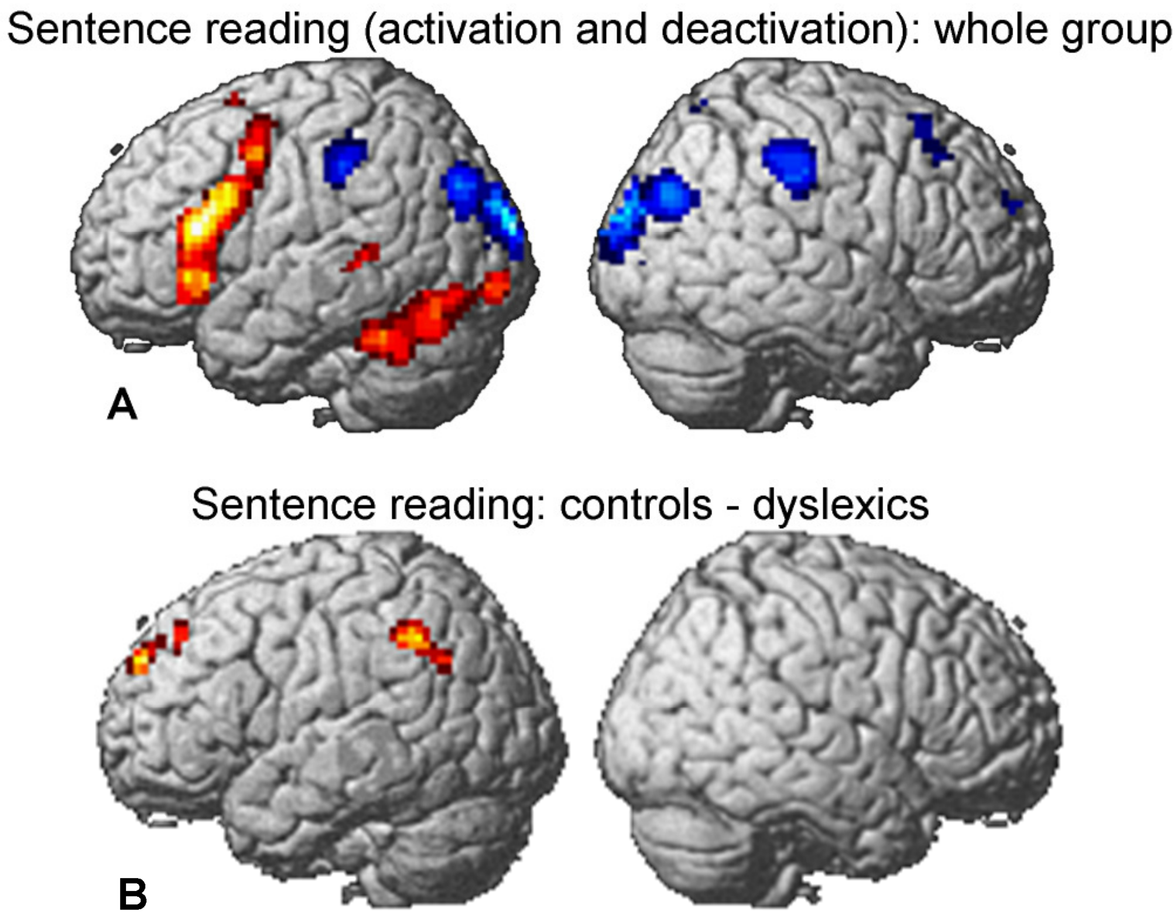


Figure 6.1. fMRI results of sentence reading.
The whole group fMRI analysis (one-sample t-test, $p < 0.05$, FWE corrected) revealed that the children activated a predominantly left-hemispheric language network during sentence reading that included inferior frontal, middle temporal, and inferior occipito-temporal regions (A: red). The reverse contrast indicated "default" activation (i.e. larger activation during baseline than during sentence reading) mainly in posterior occipito-parietal regions (A: blue). The group contrast (2-sample t-test, $p < 0.001$ uncorrected) between dyslexic and normal reading children revealed decreased activation in frontal and inferior parietal regions of the left hemisphere for children with dyslexia (B).

ROI analyses. Additional group comparisons (t-tests) were computed for ROIs based on the previously published effects of dyslexia during sentence reading (Kronbichler et al., 2006; McCandliss et al., 2003; Meyler et al., 2007). Dyslexic children showed less activation than control children in the VWFA ($t(1,32) = 2.8$, $p < 0.05$) and in both ROIs of the middle temporal gyrus (more anterior/Meyler: $t(1,32) = 3.0$, $p < 0.01$; more posterior/Kronbichler: $t(1,32) = 2.4$, $p < 0.05$).

Table 6.3. Sentence reading activation in fMRI (whole group and group differences)

cluster size	t	x	y	z	Location	BA
Sentence reading vs. baseline (whole group)						
612	10.21	-42	10	27	Inferior Frontal Gyrus	9
	9.54	-45	21	16	Inferior Frontal Gyrus	45
	8.46	-33	23	-6	Inferior Frontal Gyrus	47
268	8.63	-42	-45	-20	Fusiform Gyrus	37
	8.54	-33	-93	0	Middle Occipital Gyrus	18
	7.56	-42	-62	-12	Fusiform Gyrus	37
204	8.31	-3	14	55	Superior Frontal Gyrus	6
30	6.14	33	26	-4	Inferior Frontal Gyrus	47
23	5.94	-24	-59	42	Superior Parietal Lobule	7
	5.93	-24	-47	44	Precuneus	7
18	5.77	-56	-38	5	Middle Temporal Gyrus	22
	5.69	-50	-43	10	Middle Temporal Gyrus	21
Sentence reading vs. baseline (controls vs. dyslexics)						
200	5.52	-9	44	14	Medial Frontal Gyrus	10
	5.46	-6	51	25	Superior Frontal Gyrus	9
	3.79	-12	40	37	Medial Frontal Gyrus	8
70	4.83	-53	-45	41	Inferior Parietal Gyrus	40
	3.76	-50	-60	33	Angular Gyrus	39
14	3.93	-12	-45	33	Precuneus	31

Semantic processing during sentence reading

All children. In the whole group voxel-based fMRI analysis of the incongruency effects, incongruous sentence endings lead to increased activation compared to congruous endings in inferior frontal and superior temporal areas of the left hemispheric language network ($p<0.001$, uncorrected; Table 6.4, Figure 6.2A).

More activation for congruous than for incongruous endings were mainly found bilaterally within large portions of the superior frontal and the parietal lobe: the precuneus, the inferior parietal lobe, the cingulate gyrus, the middle frontal gyrus and the superior frontal gyrus of both hemispheres; as well as the right supramarginal gyrus and the right medial frontal gyrus ($p<0.001$, uncorrected; Table 6.4, Figure 6.2A).

Group contrasts. Dyslexic children showed reduced incongruency effects in the left inferior parietal cortex and in the precuneus compared to controls ($p < 0.001$ uncorr., Table 6.4, Figure 6.2B), but they did not show an increased incongruency effect in any region.

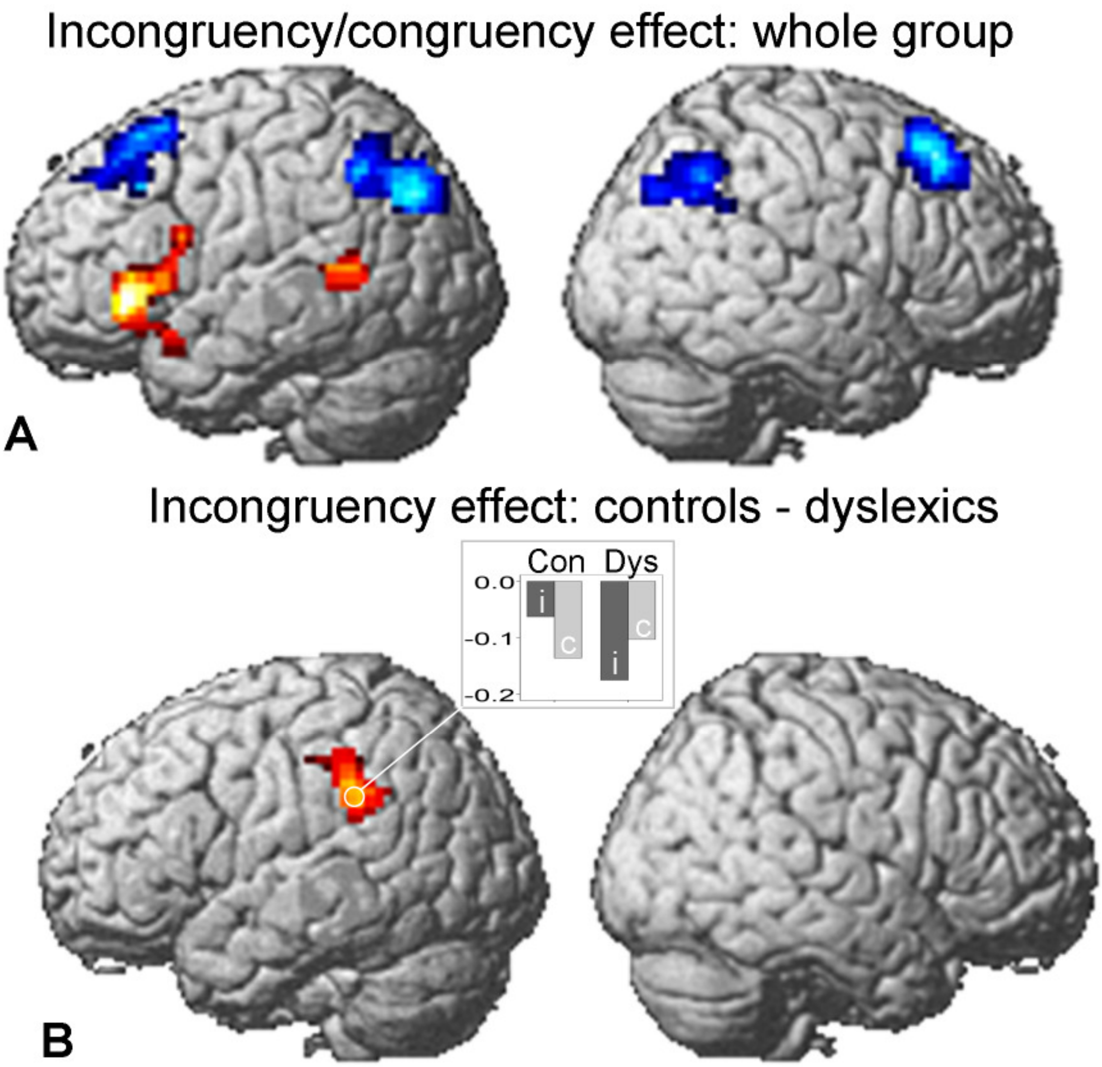


Figure 6.2. fMRI results of the incongruency effect.
The whole group fMRI analysis for the incongruency contrast (incongruous vs. congruous sentence endings, $p < 0.001$, uncorrected) revealed increased activation for incongruous relative to congruous endings in inferior frontal and superior temporal areas within the left hemisphere (red). Increased activation for congruous compared to incongruous (blue) sentence endings was found bilaterally in inferior parietal and middle/superior frontal regions, as well as in precuneus and cingulate regions (A). Dyslexic children showed reduced incongruency effects ($p < 0.001$, uncorrected) compared to controls in the supramarginal gyrus of the left inferior parietal cortex and in the precuneus (B). This effect reflected a group-specific pattern of differential deactivation for incongruous (i) and congruous (c) endings mainly due to increased deactivation following incongruous endings for the dyslexic (Dys) compared to the control (Con) children.

Reading speed covariate. The voxel-based analysis with reading speed as a covariate including all 38 children revealed an increased incongruency effect with increasing reading speed that corroborated the main effects from the group comparison. We found activations in the inferior parietal gyrus and the precuneus, and additionally in the supramarginal gyrus, the inferior temporal gyrus, the cuneus and the transverse temporal gyrus (Supplemental Material, Fig. 6.1B; $p < 0.001$

uncorr., Supplemental Material, Table 6.3). We did not find any region negatively correlated with reading skills for the same analysis.

ROI analyses. We computed separate Analyses of Variance with the within subject factors “incongruency” (incongruous vs. congruous) and “dyslexia” (dyslexic vs. controls) for the literature-based ROIs and for the ROIs based on the local maxima from the incongruency group comparison (Table 6.4).

In the VWFA ROI (−43/ −54/ −12) and in the more anterior middle temporal ROI (Meyler et al., 2007), the dyslexic children showed generally reduced activation compared to the controls (VWFA: $F(1,32) = 8.9$, $p<0.01$; MT: $F(1,32) = 7.5$, $p<0.05$), but these group main effects were not modulated by “incongruency”, nor were there any “incongruency” main effects (all F’s < 1).

In the more posterior middle temporal ROI (Kronbichler et al., 2006), the dyslexia main effect was less robust ($F(1,32) = 4.0$, $p<0.1$), but there was a trend for a “incongruency” by “dyslexia” interaction ($F(1,32) = 4.1$, $p<0.1$). The incongruency main effect was not significant ($F<1$).

In the inferior parietal ROI from the voxel-based group comparison, there was a strong “incongruency” by “dyslexia” interaction ($F(1,32) = 23.3$, $p<0.001$), whereas both main effects were not significant (both F’s < 1). This interaction was due to a relative activation increase for incongruous compared to congruous endings in controls ($t(1,21) = 3.9$, $p<0.001$), but also due to a activation decrease for incongruous compared to congruous endings in dyslexic children ($t(1,11) = -3.2$, $p<0.01$). This effect was mainly due to a differential response to incongruous endings, as the two groups did not differ for congruous endings ($t < 1$), but tended to differ for incongruous endings ($t(1,32) = 2.0$, $p<0.1$) with control children showing relatively more activation than children with dyslexia.

In the precuneus ROI from the voxel-based group comparison, there was decreased activation for incongruous compared to congruous endings ($F(1,32) = 13.0$, $p<0.01$), especially in the dyslexic children ($F(1,32) = 14.6$, $p<0.001$). The dyslexia main effect was not significant ($F < 1$).

Table 6.4. fMRI incongruency effect (whole group and group differences)

Incongruency effect (whole group)						
Cluster size	t	x	y	z	Location	BA
incongruous – congruous						
223	4.90	-45	29	-4	Inferior Frontal Gyrus	47
	4.06	-48	11	-16	Superior Temporal Gyrus	38
	4.04	-53	15	5	Inferior Frontal Gyrus	45
58	4.11	-48	-49	11	Superior Temporal Gyrus	39
congruous - incongruous						
353	5.95	-36	-77	43	Precuneus	19
	4.07	-50	-56	50	Inferior Parietal Lobule	40
	3.88	-53	-50	44	Inferior Parietal Lobule	40
1244	5.55	-9	-60	33	Precuneus	7
	5.53	-3	-30	35	Cingulate Gyrus	31
	5.46	-9	-57	25	Cingulate Gyrus	31
292	5.15	-27	26	54	Superior Frontal Gyrus	8
	4.57	-18	29	46	Superior Frontal Gyrus	8
	4.24	-24	28	37	Middle Frontal Gyrus	8
280	5.01	27	29	51	Superior Frontal Gyrus	8
	4.84	24	34	40	Middle Frontal Gyrus	8
205	4.42	45	-53	44	Inferior Parietal Lobule	40
	4.32	42	-71	37	Precuneus	19
	3.67	45	-45	30	Supramarginal Gyrus	40
39	3.68	9	44	12	Medial Frontal Gyrus	10
Incongruency effect (controls vs. dyslexics)						
129	4.99	-59	-39	32	Inferior Parietal Lobe	40
58	3.72	3	-47	55	Precuneus	7

6.4.3 ERP results

Sentence reading

Segmentation. The grand mean of all words during sentence processing showed 3 pronounced GFP peaks (see Fig. 6.3A) between 86 and 422 ms. Topographic clustering revealed that the 3 GFP peaks corresponded to 3 microstates with distinct topographies, the P1 (86-151 ms), the N1 (152-280 ms), and the P2 (281-422 ms) (Fig. 6.3B).

Map analyses. The P1 maps were topographically different between dyslexic and control children (TANOVA-norm, $p<0.05$; TANOVA-raw, $p<0.1$). They were not different regarding map strength (GFP: $t(1,45)=0.7$, $p>0.2$). The t-maps in Figure 6.3C illustrate that the topographic differences were due to the central negativity extending more laterally in controls than in dyslexic children as indicated by significant differences at left and right temporal electrodes.

No group differences were found for the N1 maps (GFP, TANOVA-raw, and TANOVA-norm, all $p>0.2$). Although the t-maps for the group comparison in the P2 segment showed focal differences at a few posterior electrodes suggesting a more right lateralised P2 in dyslexics, the spatial analysis could not confirm significant differences (GFP and TANOVA-raw, both $p>0.2$; TANOVA-norm, $p>0.11$).

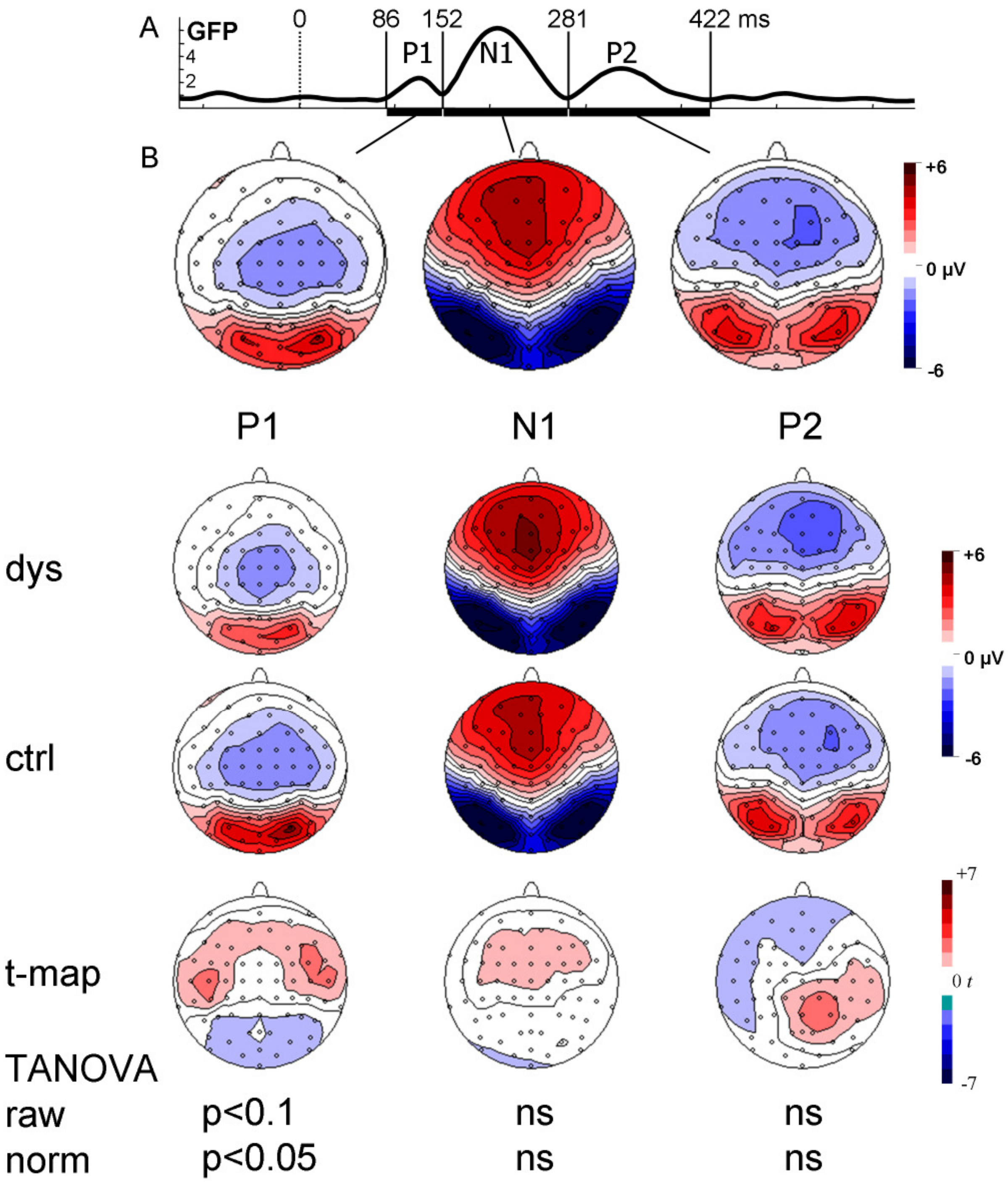


Figure 6.3. ERP results of sentence reading.
The ERP response to all words in a sentence consisted of 3 clear GFP peaks (A), which corresponded to 3 microstates with stable topographies (B). The ERP maps of the children

with dyslexia (dys) and of the controls (ctrl) differed in the P1 microstate (TANOVA, t-map), but not in the N1 and P2 microstate (TANOVA) (C).

Map latencies. The latency analyses based on map templates (TCR) revealed no significant latency differences between the two groups for the P1 and the P2 microstates. However, the N1 microstate tended to be delayed in dyslexic children compared to controls ($t(1,44.5)=1.8$, $p<0.1$). As the P1 microstates differed topographically between dyslexic children and controls, we ran the latency analysis also with a P1 template derived from the average of the normalised P1 maps from dyslexic children and controls. This analysis yielded no significant difference ($p>0.2$). Similar results were obtained with correlations between latency measures and reading skills (correct words per minute). No significant correlations were found for the P1 ($r=-0.10$) and the P2 ($r=-0.06$) segments. There was a weak trend towards delayed N1 latencies with slower reading ($r=-0.23$, $p<0.11$) similar to the result in the group comparison.

Semantic processing during sentence reading

Segmentation. Incongruous sentence endings were processed differently ($p < 0.01$) from congruous endings in two time windows between 246 and 543 ms (N400) and between 617 and 1125 ms (late positivity, LP), as revealed by the TANOVA analysis across the entire group (Figure 6. 4A). Topographic clustering of the difference maps (incongruous ERP minus congruous ERP) divided each of these time windows in two parts (for the raw maps see supplementary Figure 6.3), resulting in 4 microstates subsequently used for analysis: N400a (246-319 ms), N400b (320-543 ms), LPa (617-831 ms), and LPb (832-1125 ms). The difference maps (incongruous ERP minus congruous ERP) for the 4 microstates are illustrated in Figure 6.4B.

Map description. The early N400 effect microstate (N400a) showed a strongly left-lateralised topography with posterior negativity and anterior positivity (Figure 6. 4B) In the late N400 effect microstate (N400b) the posterior negativity and the anterior positivity were less clearly lateralised. The two microstates with the late posterior positivity showed more distinct topographies. The positivity was bilaterally more inferior, but with a left-lateralised tendency in the earlier part, and was more superior and central, although still slightly left-lateralised, in the later part.

Map analyses. The early N400 effect microstate (N400a) did not differ between dyslexic children and controls (GFP, TANOVA-raw, and TANOVA-norm, all $p>0.2$). The later N400 microstate (N400b), however, was reduced (TANOVA-raw, $p<0.05$) and topographically distinct (TANOVA-norm, $p<0.05$) in dyslexic children compared to controls. GFP did not differ between the groups in this segment ($p>0.2$). The t-maps in Figure 6.4C illustrate that these N400 differences were due to reduced posterior negativity and anterior positivity in the dyslexic children.

The ERP maps during the first segment of the late posterior positivity were not different between dyslexic children and controls (GFP, TANOVA-raw, and TANOVA-norm, all $p>0.2$). During the second segment of the late posterior positivity, the t-maps showed focal group differences, at parietal and right temporal electrodes, but these differences did not quite reach significance in the mapping analyses (GFP and TANOVA-raw: $p>0.2$; TANOVA-norm: $p=0.10$).

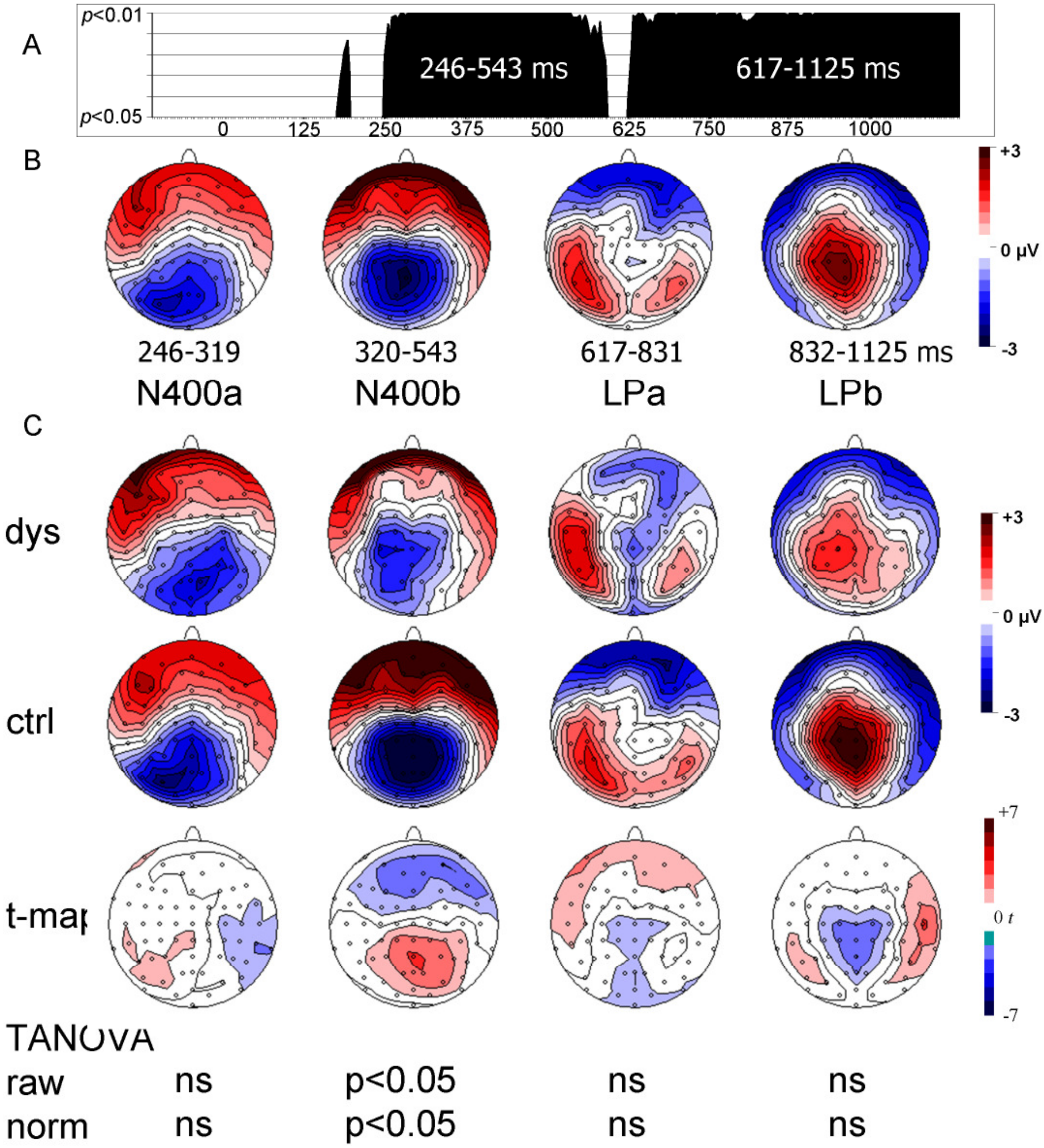


Figure 6.4. ERP results of the incongruency effect.
Incongruous and congruous sentence endings were processed differently during two time windows (A), each of which was further divided into 2 microstates with stable topographies (B). The difference maps (incongruous – congruous) differed between children with dyslexia (dys) and controls (ctrl) during the N400b microstate (TANOVA, t-map), but not during the other 3 microstates (TANOVA) (C).

Map latencies. The latency analyses revealed no significant differences between dyslexic children and controls (N400a, N400b, and LPa: all p>0.2; LPb: p=0.12). As the N400b microstate differed topographically between dyslexic children and controls, we ran the same analysis with an N400b template derived from the average of the normalised N400b maps from the dyslexic children and the controls.

The analysis yielded no significant difference ($p>0.2$). Similarly, no significant correlations between latency measures and reading score (correct words per minute) were obtained for the N400a ($r=0.01$), N400b ($r=-0.06$), and LPa (-0.09) segments. Only the LPb topography tended to be delayed with slower reading (-0.25, $p<0.1$).

Pz Analyses. Analogous to the fMRI ROI analysis we computed one ANOVA per microstate with the within subject factors “incongruency” (incongruous vs. congruous) and the between subject factor “dyslexia” (dyslexic vs. control) for the amplitudes at Pz.

In the N400a segment incongruous endings elicited less Pz-positivity than congruous endings ($F(1,45)=20.4$, $p<0.001$). Neither the dyslexia main effect nor the dyslexia-by-incongruency interaction were significant (both F’s < 1). Planned comparisons also did not reveal any group differences, neither for congruous ($t=-0.5$) nor for incongruous ($t=-1$) endings.

In the N400b segment incongruous endings also elicited less positivity than congruous endings (incongruency, $F(1,45)=46.4$, $p<0.001$), but this effect was more pronounced in control children than in children with dyslexia (incongruency x dyslexia, $F(1,45)=10.6$, $p<0.01$). The dyslexia main effect was not significant ($F<1$), Planned comparisons revealed a group difference for incongruous endings with Pz-negativity in controls but positivity in those with dyslexia ($t(1,45) = -2.4$, $p<0.05$), but not for congruous endings ($t=0.8$). The waveforms (supplementary Figure 6.3) illustrate a negative-going peak during the N400b segment for congruous endings, and a negative peak for incongruous endings which was more negative in controls than in dyslexic children.

In the LPa segment there was a main effect of dyslexia ($F(1,45)=8.1$, $p<0.01$), indicating more positive values for control children compared to children with dyslexia. Neither the incongruency main effect ($F<1$) nor the incongruency-by-dyslexia interaction ($F<1.4$) were significant. Planned comparisons revealed group differences for both incongruous ($t(1,45)=2.8$, $p<0.01$) and congruous ($t(1,45)=2.2$, $p<0.05$) endings.

In the LPb segment incongruous endings elicited more positive values at Pz than congruous endings ($F(1,45)=43.2$, $p<0.001$), especially in controls (incongruency x dyslexia, $F(1,45)=9.3$, $p<0.01$). Planned comparisons revealed no groups differences when testing the conditions separately (incongruous: $t(1,45)=1.5$, $p>0.13$; congruous: $t(1,45)=-1$).

Source localisation

Estimating the sources of the grand mean over all 52 subjects at GFP peaks of the N400b and the late positivity using LORETA and LAURA both suggested a source distribution in the left hemisphere that included inferior frontal and middle temporal regions corresponding to the fMRI activation (Figure 6. 5). While anterior middle temporal sources were stronger for the N400 component, inferior frontal and posterior middle temporal sources were relatively stronger in the late positivity component.

In order to examine the correspondence between statistical characterizations of the local EEG and fMRI incongruency effects, we computed EEG source statistics for selected voxels: those voxels showing local source maxima of the grand mean incongruency effect, plus the voxel corresponding to the inferior parietal fMRI activation. To this end, current source density at the N400b and the LP GFP peak was compared to baseline (at time 0, before systematic incongruency effects are expected, using t-tests). As indicated in Figure 6.5, the inferior frontal ($t(1,51)=2.15$, $p<0.05$) and posterior temporal activation ($t(1,51)=3.11$, $p<0.01$) was significant for the late positivity, and the anterior temporal activation approached significance ($t(1,51)=1.65$, $p<0.11$) for the N400b using the LORETA algorithm. The LAURA algorithm did not yield any significant results despite its similar grand mean source distribution, suggesting that the two methods mainly differ in susceptibility to individual variation. In those voxels showing such significant N400b or late positivity effects compared to baseline, we tested whether the groups would differ, but found no significant differences (all $p >.02$).

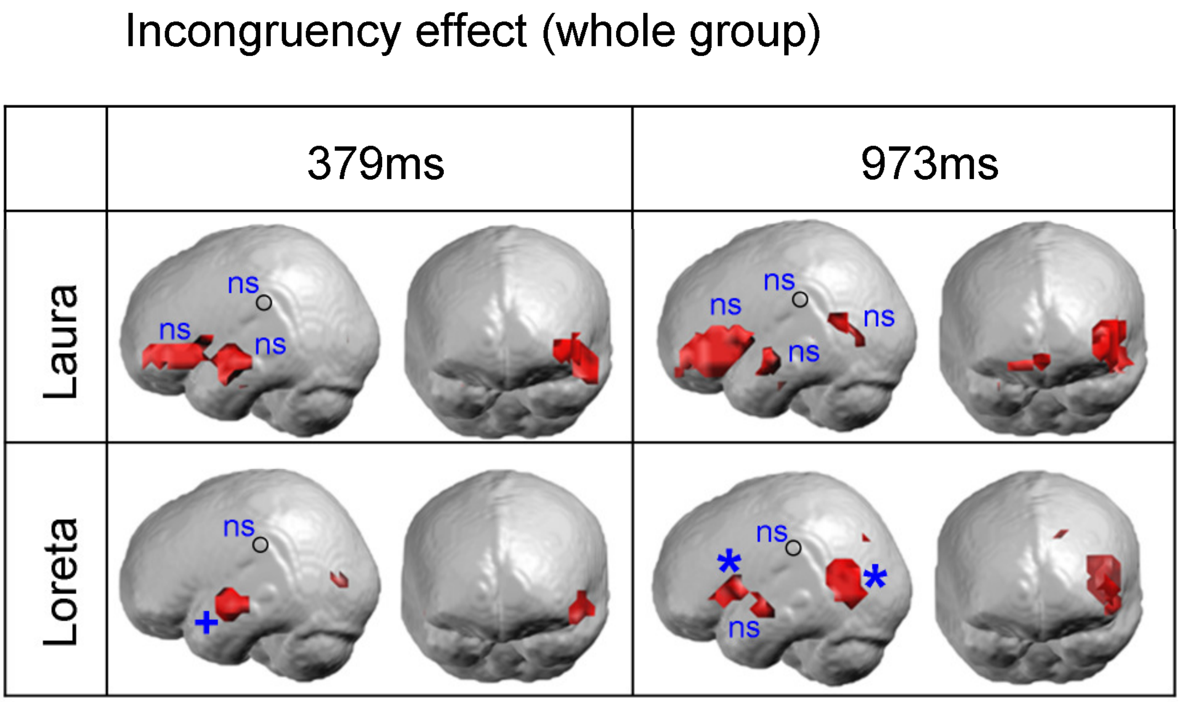


Figure 6.5. LAURA and LORETA source localisations
The source distributions of the N400b GFP peak (at 379ms) and the LP GFP peak (at 973 ms) were estimated using the LAURA and LORETA algorithms. Across the whole group of children the inverse solutions revealed a network consisting of inferior frontal and temporal regions. The anterior middle temporal sources of the N400 were reduced in the late positivity, while inferior frontal and posterior temporal sources increased. Current source density at these time points were tested vs time zero in the voxels showing local maxima for the grand mean incongruency effect: LAURA: -53, -6, -10 (middle temporal gyrus); -45, 48, -4 (middle frontal gyrus); -49, -62, 7 (middle temporal gyrus). LORETA: -52, -6, -5 (superior temporal gyrus); -49, -62, 7 (middle temporal gyrus); -50, 14, 10 (precentral gyrus) and in inferior parietal cortex showing the fMRI group incongruency effect (-59, -39, 32). Significance of the effects is indicated in the figure (*: $p<0.05$, +: $p<0.11$; ns: not significant).

6.4.4 Correlations between dyslexia effects in fMRI and ERPs

The incongruency effect in the inferior parietal ROI (-59/ -39/ 32) was significantly correlated with the N400 effect at the Pz electrode ($r=-0.40$, $p<0.05$), but not with the amplitude in the P1 Segment at electrode O2' ($r=-0.10$, p=ns). In addition, the inferior parietal incongruency effect was also correlated with the group effects for generic sentence reading in the fMRI ROIs (medial frontal: $r=0.58$, $p<0.001$; superior frontal: $r=0.42$, $p<0.01$; inferior parietal: $r=0.27$, $p<0.1$).

The correlation between the amplitude of the N400 effect and the incongruency effect in inferior parietal region is also supported by an additional voxel-based analysis of the incongruency effect in which the Pz amplitude of the N400 effect was used as a covariate of interest. The cluster with the most significant effect ($p<0.001$) was found in the inferior parietal region (Supplementary Material Figure 6.4).

6.5 Discussion

The present study investigated deviant brain processes in dyslexic children during sentence reading with a focus on semantic processing. By combining the advantages of fMRI and ERP techniques we sought to characterise distribution and dynamics of neural impairments.

6.5.1 Sentence reading and semantic processing across all children

The children activated a left-lateralised network while reading sentences. The activation in inferior frontal, middle temporal, and fusiform regions is in good agreement with an earlier study investigating sentence reading in adolescents (Kronbichler et al., 2006), and with a recent meta-analysis depicting the language network activated in various sentence or text processing tasks (Vigneau et al., 2006).

Also, the P1-N1-P2 sequence in the ERP elicited by all words in the sentences is typical for early components in response to visual word stimuli in children (Brandeis et al., 1994; Maurer et al., 2006) as well as in adults (Brandeis et al., 1995; Brandeis et al., 1994; Brem et al., 2006; Maurer et al., 2005a; Maurer et al., 2005b). The absence of prominent GFP peaks after 400ms suggests that averaging over the different word positions and classes largely eliminated later components, which were analysed in more detail for incongruous and congruous sentence endings.

The children in the present study showed increased activation for incongruous compared to congruous sentence endings in inferior frontal and superior temporal areas (anterior and posterior part). Inferior frontal modulation by contextual expectation has been previously reported in fMRI studies of sentence processing in adults (Baumgaertner et al., 2002; Kiehl et al., 2002). The weaker modulations in temporal regions also agree with adult work by Baumgaertner et al. (2002) for (posterior) middle temporal regions (slightly different from our superior temporal activation) and by Kiehl et al. (2002) for (superior) anterior temporal regions.

Since other developmental fMRI studies on sentence processing did not examine effects of semantic priming (Kronbichler et al., 2006; Meyler et al., 2007), the present study is the first to indicate that children activate similar regions as adults during semantic processing in sentence reading.

Interestingly, there were also sizeable regions with more activation for congruous than incongruous sentence endings, including the bilateral parietal cortices, and the precuneus. These regions have been shown to be deactivated during sensory tasks, and it has been suggested that they belonged to a default network that is activated during rest (Halder et al., 2007; Raichle et al., 2001). The functional role of the default network is not entirely clear, but a role in memory processes has been proposed, as similar areas are activated during successful memory retrieval (Buckner et al., 2005).

The congruency effects in the parietal and precuneus regions were due to reduced deactivation for congruous than incongruous endings (compare also Figure 6.1), and thus modulated overall deactivation in this region. Such modulation may occur because the same processes that are active during baseline are relatively more active during the congruous than during the incongruous condition. As default activation has been linked to successful memory integration (Buckner et al., 2005), a reduced level of deactivation during the congruous condition may reflect the same active process as during baseline, but not in the incongruous condition where successful memory integration is hardly possible.

Alternatively, a process that is different from the one responsible for relative activation during baseline may be involved, and reflect increased language-specific or attentional engagement for congruous endings (Kuperberg et al., 2003).

Thus, the incongruency and the congruency fMRI effects may reflect different aspects of semantic processing, effects of semantic access in inferior frontal and temporal regions, and effects of semantic integration in bilateral parietal and precuneus regions. Alternatively, however, a different degree of deactivation in these parietal regions may result from the extent to which attentional resources are allocated in a sentence task, as suggested by Kuperberg et al. (2003).

Incongruency of the sentence ending strongly modulated the ERP to the last word starting at about 240 ms. A posterior positive and anterior negative topography was stronger for congruous than for incongruous endings, resulting in a centro-parietally negative N400 effect for the difference between incongruous and congruous endings. This N400 effect could be topographically differentiated into an earlier more left-lateralised and inferior N400a negativity, and a later more central and superior N400b negativity centred around 400 ms (e.g. (Brandeis et al., 1995; Brandeis et al., 1994; Kutas and Hillyard, 1980). The later N400b effect showed a consistent (difference-) topography even though the topographies of the incongruous and congruous ERPs changed from negative/negative-going to positive over centroparietal channels (see waveforms in supplementary Figure 6. 3). Such an N400 effect with its typical centro-parietally negative distribution marks semantic integration processes during sentence reading (Friederici, 2004; Kutas and Federmeier, 2000).

A second phase of differential processing started after 600 ms with posterior positivity that was also located more inferior with a left-lateralised tendency in an earlier microstate and more superior in a later microstate. The late positive effect after 600 ms presumably corresponds to the P600 effect that has been associated with congruency judgement during sentence processing (Kolk et al., 2003; Sabisch et al., 2006). Processing related to congruency judgement can be expected to occur in the present experiment also for sentences to which children do not respond, because the rare response prompts occurred only some time after a sentence was presented.

The distributed sources of semantic components indicated by inverse solutions of GFP peaks are in excellent agreement with our fMRI results. While the anterior temporal N400 sources corroborate earlier EEG and MEG studies on sentence reading (see van Petten and Luka, 2006 for a review), the additional inferior frontal sources suggest that the corresponding activation in the fMRI data starts within 400 ms. A link between inferior frontal / anterior temporal fMRI activation and the N400 effect was also made in a previous multimodal sentence reading study on pragmatic anomalies using ERPs and fMRI (Kuperberg et al., 2003). Inferior frontal activation seems to continue and even increase during the later time segments, as indicated by the source localization of the late positivity. In addition to the increase in frontal activation there was also an increase of posterior temporal activation which was reflected in both source localization methods.

While the combined use of the EEG and fMRI methods provided complementary information regarding timing and localization of semantic effects in the present study, these effects may be somewhat underestimated because the repetition inherent in the sequential design leads to a reduced N400 (Besson and Kutas, 1993). Future studies using simultaneous EEG and fMRI recordings that do not require repetitions should thus be more sensitive for neural characteristics of semantic processing during sentence reading in the spatiotemporal domain.

6.5.2 Effects of dyslexia during sentence reading and semantic processing

The inferior parietal reduction of activation during generic sentence reading in children with dyslexia compared to controls at -53 -45 41 (and extending into the angular gyrus -50 -60 33) is in good agreement with earlier studies (supramarginal gyrus at -60 -42 30 in Kronbichler et al. (2006); angular gyrus at Tal.: -36 -62 33 in Meyler et al. (2007)). It has been suggested that underactivation in this temporo-parietal region might reflect the phonological processing deficit (McCandliss et al., 2003; Temple et al., 2001), but other explanations have also been put forward, such as a deficit in orthographic-phonological translation (Shaywitz et al., 2002), or verbal working memory or semantic integration deficits (Booth et al., 2007). The involvement of other than phonological impairments (Meyler et al., 2007) for reduced inferior parietal activation (Kronbichler et al., 2006; Meyler et al., 2007) seems likely, as the German dyslexics were not impaired in phonological processing, and showed rather a deficit in reading fluency (Kronbichler et al., 2006).

The design of the present study allowed us to investigate the role of semantic processes more directly by experimental contrasts. Dyslexic children showed a reduced difference between semantically incongruous minus congruous sentence endings in the inferior parietal region than controls. Although this area was slightly more anterior than the dyslexia effect in the analysis of generic sentence reading, it covered most of the supramarginal gyrus area reported by Kronbichler et al. (2006) thus suggesting that the reduced inferior parietal activation during sentence reading is due to a semantic impairment.

Such an interpretation in terms of semantic processing deficits is consistent with the N400 literature (Kutas and Federmeier, 2000; van Petten and Luka, 2006). The location of this impairment in inferior parietal cortex during sentence reading in dyslexia is also in agreement with the finding that the correlation between semantic association within word pairs, and activation in inferior parietal region was weaker in dyslexics than controls (Booth et al., 2007), thus supporting the interpretation of a semantic impairment.

However, the possibility can not be excluded that priming of sentence endings in the present experiment extends - in addition to semantics - also to phonology or orthography. Such an interpretation would still mean that dyslexic children are not only impaired in basic word recognition mechanisms, but that they are also impaired in integration at the sentence level, or in using sentence context for reading.

As the group difference in the incongruency contrast represents a double difference, the ROI analyses which consider the percent signal change relative to baseline are important for the interpretation of the effects.

The group incongruency effects in both the inferior parietal and precuneus regions reflect a modulation of an overall deactivation compared to baseline. As we have discussed for the congruency effects of the whole group analysis, such a pattern can still reflect differences in active brain processes, with less deactivation characterising the more active condition, and possibly involving processes which are also functional at “rest” during baseline.

An alternative explanation for the incongruency group effect of the inferior parietal difference is that it reflects a group difference of a congruency effect in nearby lateral parietal and precuneus regions, and might thus be related to the default mode or to memory retrieval effects (Buckner et al., 2005). Following this explanation dyslexic children would show a larger congruency effect than control children due to increased deactivation for incongruous endings. The ROI analysis for the inferior parietal effect lends credit to both possibilities as the significant interaction between group and incongruency was based on a significantly larger activation for incongruous than congruous endings in the control children and significantly larger activation for congruous than incongruous endings in the dyslexic children.

In the precuneus, however, the ROI analysis for the incongruency group effect seems to favour the second explanation, as the interaction between group and incongruency reflected a larger activation for congruous than incongruous endings in dyslexic children, whereas the two types of sentence endings were associated with a similar level of activation in the control children in this region.

Although in the present case the baseline included the first 3 words of the sentence, and signal decrease differs from typical deactivation, earlier studies have reported reduced activation in dyslexic children and adolescents compared to controls in this inferior parietal region, which was mainly due to a deactivation in relation to baseline in the dyslexic group (Hoeft et al., 2006; Hoeft et al., 2007). Interestingly, the same inferior parietal region showed also a reduction of gray matter in dyslexic adolescents compared to both age-matched and reading-level-matched controls (Hoeft et al., 2007), which points to a critical role of this region for the development of dyslexia. Our results suggest that dysfunction in this inferior parietal region, and possible gray matter anomalies, does not only affect phonological processing, but also semantic processing during sentence reading.

In addition to the inferior parietal effect of dyslexia during sentence reading, decreased activation in children with dyslexia compared to controls was found in superior frontal areas. Although no significant group differences were reported for this region in the two previous studies on sentence reading (Kronbichler et al., 2006; Meyler et al., 2007), control children in the Kronbichler study showed activation in a similar superior frontal region, which was absent in the dyslexic participants. The more robust effect in the present study may be related to the way the sentences were presented. In the two previous studies more complex sentences with all words of a sentence presented simultaneously were used, whereas in the present study the simple sentences were presented word by word requiring the first words of the sentence to be kept in mind. This may have led to higher demands on working memory in the present study increasing differences between dyslexics and controls. This is in agreement with a recent study showing that high demand on phonological working memory leads to activation differences between participants with and without dyslexia in a nearby superior frontal region (Vasic et al.).

However, as the children in the present study were younger than the participants in the Kronbichler study, more robust dyslexia effects in superior frontal regions may be found at a younger age during sentence reading tasks.

While our dyslexia effects during sentence reading in inferior parietal areas agree with two previous studies (Kronbichler et al., 2006; Meyler et al., 2007), the voxel based analysis could not replicate group differences in the middle temporal gyrus found in both these studies. The less robust temporal effects in our study compared to the two other studies may again be related to the difference in stimulus material or presentation mode.

However, we found a similarly reduced activation for dyslexics compared to controls in the ROI analyses of left middle temporal areas using the coordinates of the Meyler and the Kronbichler study. Whereas the group difference in the Meyler ROI was not modulated by semantic incongruency, the slightly more inferior and posterior middle temporal ROI from the Kronbichler study showed a strong trend towards an interaction between dyslexia group and incongruency.

Similar to the Kronbichler study, we also found decreased activation during sentence reading in dyslexic children compared to controls in the VWFA ROI in the left inferior occipito-temporal cortex. Unlike the dyslexia effects in the inferior parietal and posterior middle temporal regions, these inferior occipito-temporal group differences were not modulated by incongruency of the sentence endings. This suggests that reduced activation in inferior occipito-temporal regions is related to general deficits of word reading in dyslexia, in agreement with studies using isolated word form or letter stimuli and reporting inferior occipito-temporal deficits (Brambati et al., 2006; Brunswick et al., 1999; Cao et al., 2006; Paulesu et al., 2001).

While the fMRI results show which dyslexia effects during sentence reading are effects of generic word reading, and which effects are modulated by semantic priming, the ERP data provide critical information about the time course of these processing deficits.

Dyslexia effects during generic sentence reading were already found in the early P1 component. A similar result of reduced P1 amplitudes was already reported in an earlier study with the same paradigm, but a different subject group (Brandeis et al., 1994), and with a different paradigm, but with partly overlapping subjects as in the present study at a different age (Maurer et al., 2007), lending support that relatively early visual processing is impaired in children with dyslexia. Such an early deficit may not be word-specific, as attenuated P1 components also occurred before learning to read (Maurer et al., 2007), or with non-language stimuli (Solan et al., 1990). The lack of N1 effects is also consistent with our previous work on sentence reading in dyslexia. The finding confirms that while single word N1 attenuations are present in younger children with dyslexia such as 2nd graders (Maurer et al., 2007), such an attenuation is no longer present in older children with dyslexia or while reading sentences for comprehension. Dyslexia effects at the N1 level for sentence reading at this age may instead manifest itself as a processing delay, as suggested by the statistical trend in the latency analysis.

Although several microstates were identified during which incongruous sentence endings were processed differently from congruous endings, only the microstate around 400 ms was also reduced in dyslexic children compared to controls. This N400 incongruency effect is typically interpreted as an effect of semantic priming by sentence context (for reviews see (Friederici et al., 2004; Kutas and Federmeier, 2000; van Petten and Luka, 2006). This indicates that dyslexic children are impaired regarding semantic integration during sentence reading starting within the first 400 ms. The reduced N400 effect in the dyslexic children in the present study is in agreement with two earlier studies covering both dyslexic children (Brandeis et al., 1994) and dyslexic adults (Helenius et al., 1999). Younger children with dyslexia had shown an even larger N400-effect than controls in one previous study (Neville et al., 1993). This suggests that the reduction of the N400-effect in dyslexic participants also develops with age, thus paralleling the effect found in the inferior parietal area for sentence reading (Meyler et al., 2007). Reduced N400 effects during sentence processing in dyslexia seems to be limited to reading tasks, as no difference in the N400 effect between dyslexic and control children at a similar age were found with sentences presented in the auditory modality (Sabisch et al., 2006).

Moreover, the group differences in the N400-effect could be attributed mainly to the incongruous endings, as the two groups differed for incongruous but not for congruous endings in this time range (Supplemental Material, Figure 6. 3). This suggests that dyslexic children hardly differ from controls while reading simple sentences with highly primed endings, but that their brain response to semantically unexpected endings is reduced. Importantly, however, this did not lead to more pronounced behavioural deficits for incongruous than for congruous endings, as the dyslexic children exhibited a similar increase of error and reaction time compared to the controls for both ending types. The absence of semantic effects at the behavioural level in this group of dyslexic children is also in agreement with their normal performance in the similarities subtest of the WISC. Further research, using additional semantic processing measures such as priming or comprehension in visual, as well as in auditory tasks, should determine whether this pattern reflects a genuine dissociation between behavioural and neural markers of semantic deficits, or whether it results from the delayed response requirement allowing for additional compensation.

Results from earlier studies (Brandeis et al., 1994; Helenius et al., 1999) indicated not only a reduced, but also a delayed N400 effect in dyslexia. In the present study there was no significant latency difference of the N400 effect. The greatly reduced size of the N400 effect in the dyslexic children resulted in a flat GFP curve and may have made the latency detection less reliable, even though a topographic correlation approach was used. This suggests that reduction and not latency delay are the most prominent characteristics of the N400 effects in this group of dyslexic children reading sentences. Alternatively, repeating the sentence reading test, as required for a sequential multimodal study, may have attenuated latency effects, consistent with effects of word frequency on component latencies in the N400 time range (King and Kutas, 1998).

While both neuroimaging modalities suggest that semantic processing during sentence reading is impaired in dyslexic children compared to controls, it takes their combination to clarify that this impairment is localised mainly to inferior parietal cortex of the left hemisphere according to the fMRI data and occurs mainly around 400 ms according to the ERP data. The correlation of the incongruency effects in inferior parietal cortex and around 400 ms, i.e. during a narrow time slot an in a small part of the active networks detected with each imaging modality, may indicate a direct relation between fMRI and ERP effects.

However, the N400 source localisation suggests that the fMRI and ERP effects are less directly related. The N400 was localised to a network including anterior temporal and inferior frontal regions, where we found no semantic group differences in the voxel-based fMRI analysis, and this network did not include the left inferior parietal cortex with the strongest semantic effects in the fMRI data. The current source density values within this fMRI-derived inferior parietal region showed no significant N400 source activation compared to baseline, but signal to noise ratio was generally low for localization of such a complex source pattern. This may also explain why the group differences in the incongruency effect significant at the scalp (Pz) could not be found at the corresponding source level. Although some left posterior activation was also evident in the N400 LORETA solution, this activation was minor and well posterior to the left inferior parietal fMRI activation. This discrepancy may be explained by different time resolutions of the two methods, and especially by the property of fMRI to integrate over distinct neural events with split-second timing differences. Thus the semantic impairment during sentence reading in dyslexia may exhibit a different behaviour over time depending on the brain region involved with more phasic activation in brain regions responsible for the N400 effect, and more sustained activation in inferior parietal cortex. While we can not exclude that the N400 source localisations are not entirely reliable, the convergence with intracranial N400 localisations, and the consistency across the two methods argue for a correct localisation.

In conclusion, the present study extends earlier results on word and sentence processing in dyslexia by showing that impairments in inferior parietal regions - unlike impairments in the inferior temporal VWFA - are modulated by semantic expectations, and co-occur with a reduction of the N400 effect. The correlation between N400 reduction and reduced inferior parietal incongruency effect in combination with N400 source localisation suggests that semantic impairment results in a N400 reduction in anterior brain regions which may be hard to detect in the hemodynamic response, and in a subsequent sustained attenuation of an inferior parietal response dominating the fMRI data.

6.6 Supplemental Material

SM Table 6.1. Behavioural results during sentence reading task.

EEG ACC	EEG RT	fMRI ACC	fMRI RT
D, F(1,45) = 10.6**	D, F(1,45) = 10.1** I, F(1,45) = 5.1*	D, F(1,32) = 18.9*** I, F(1,32) = 4.4*	D, F(1,32) = 10.8** I, F(1,32) = 5.8*

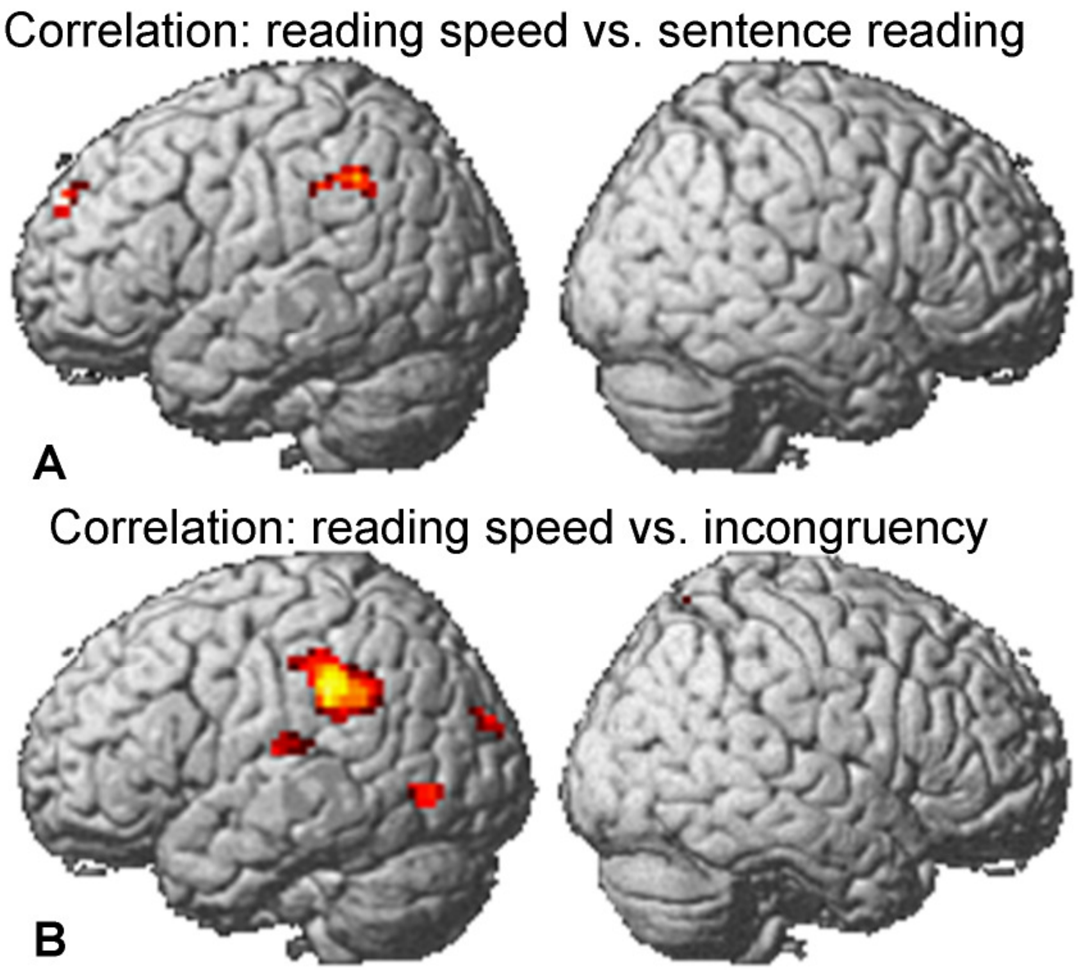
D: dyslexia, I: incongruency; *: p<0.05, **: p<0.01, ***: p<0.001.

SM Table 6.2. Correlation between reading speed and sentence reading activation in fMRI

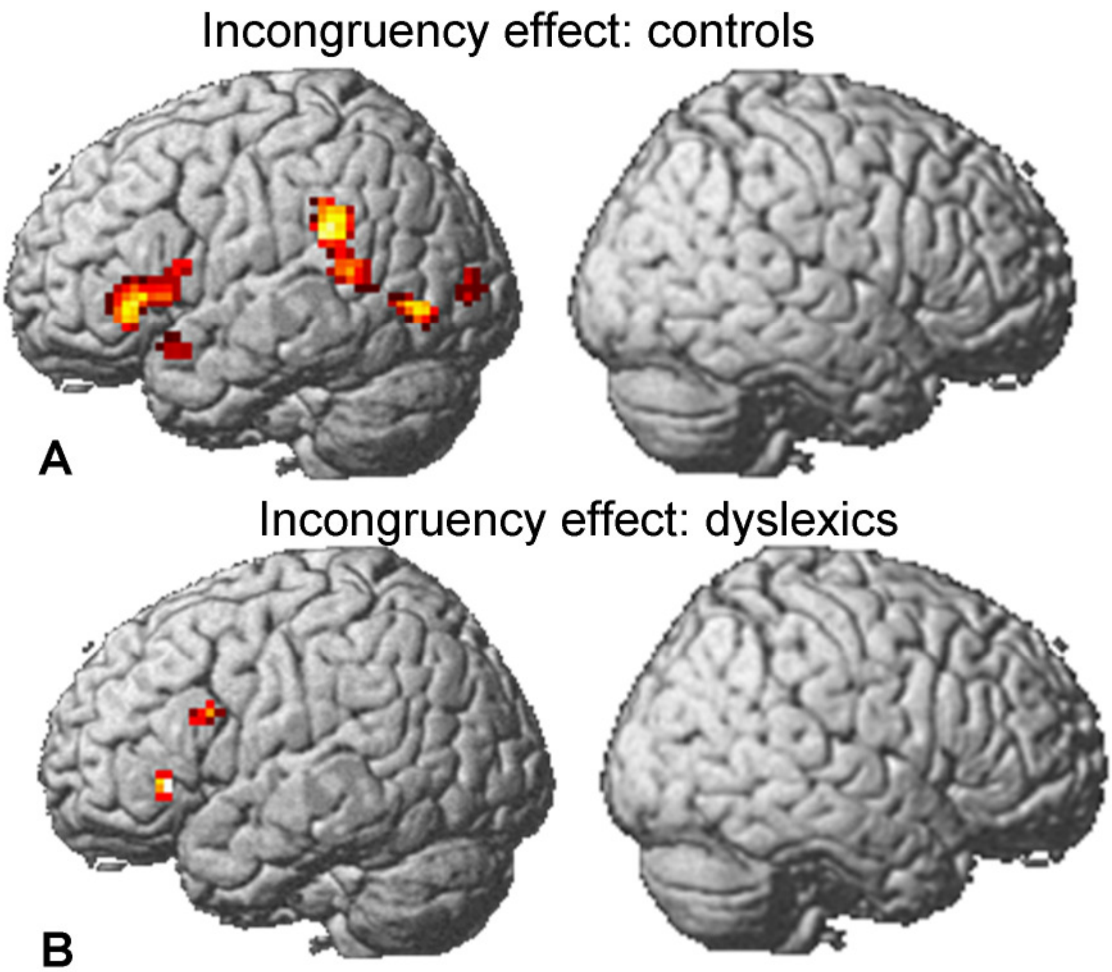
correlation reading speed vs. sentence reading						
cluster size	t	x	y	z	Location	BA
113	4.79	-6	51	25	Superior Frontal Gyrus	9
	4.07	-9	41	12	Anterior Cingulate Gyrus	32
	3.68	-18	57	28	Superior Frontal Gyrus	9
40	4.27	-50	-45	41	Inferior Parietal Lobule	40
	3.76	-59	-33	38	Inferior Parietal Lobule	40

SM Table 6.3. Correlation between reading speed and the incongruency effect in fMRI

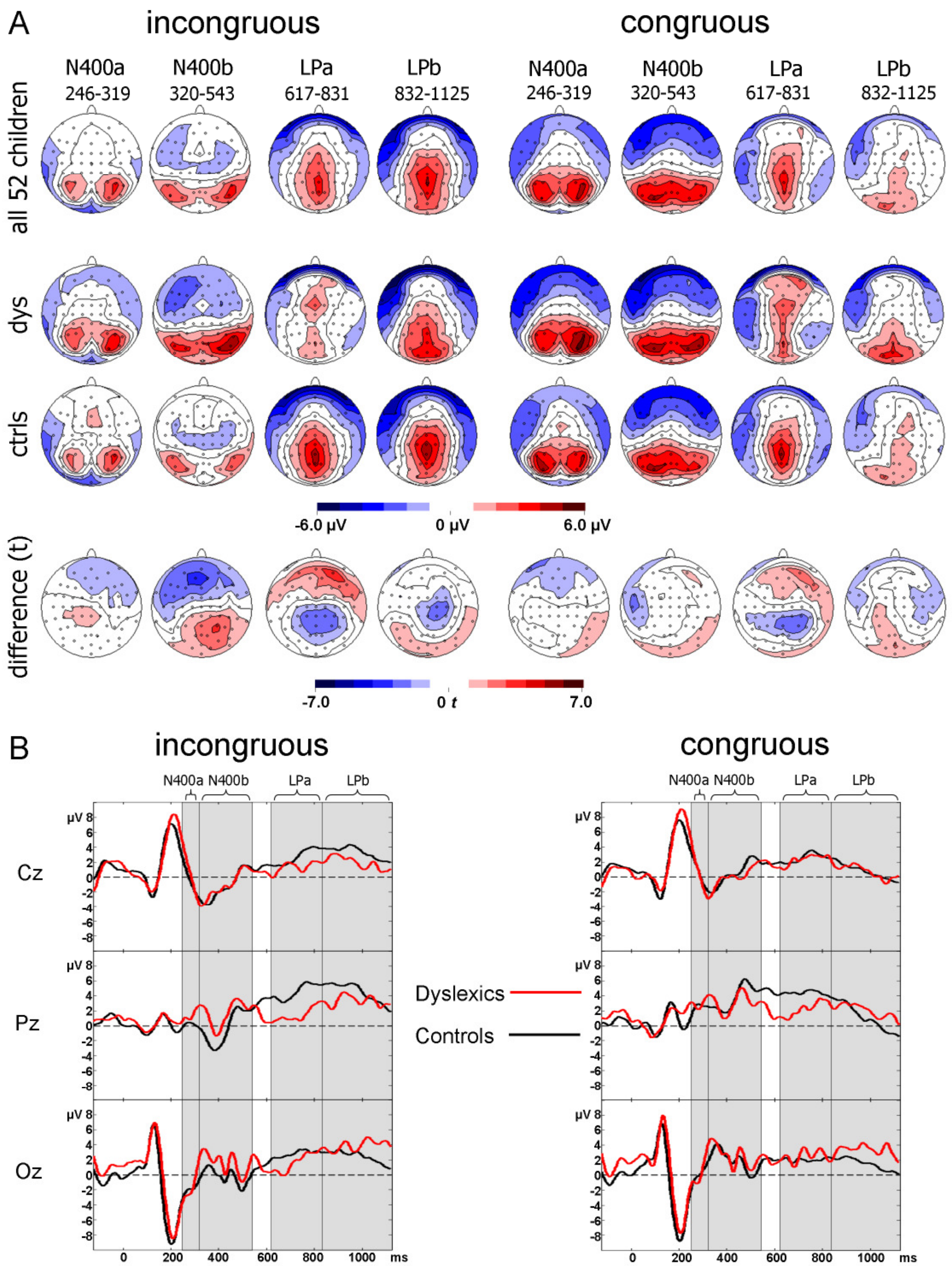
correlation reading speed vs. incongruency effect (whole group)						
cluster size	t	x	y	z	Location	BA
189	4.86	-59	-36	35	Inferior Parietal Lobule	40
	4.49	-53	-45	33	Supramarginal Gyrus	40
217	4.51	0	-47	52	Precuneus	7
	4.11	9	-50	58	Precuneus	7
	4.04	-12	-53	52	Precuneus	7
26	4.40	-45	-70	1	Inferior Temporal Gyrus	37



SM Figure 6.1. Correlation between reading speed and fMRI activation.
The correlation analyses ($p < 0.001$, uncorrected) between the reading score and fMRI activation revealed regions (A) in the superior frontal gyrus, the anterior cingulate gyrus, and the inferior parietal gyrus for sentence reading (see also SM Table 6.2), and (B) for the incongruency effect in the inferior parietal gyrus, the supramarginal gyrus, the precuneus and the inferior temporal gyrus.



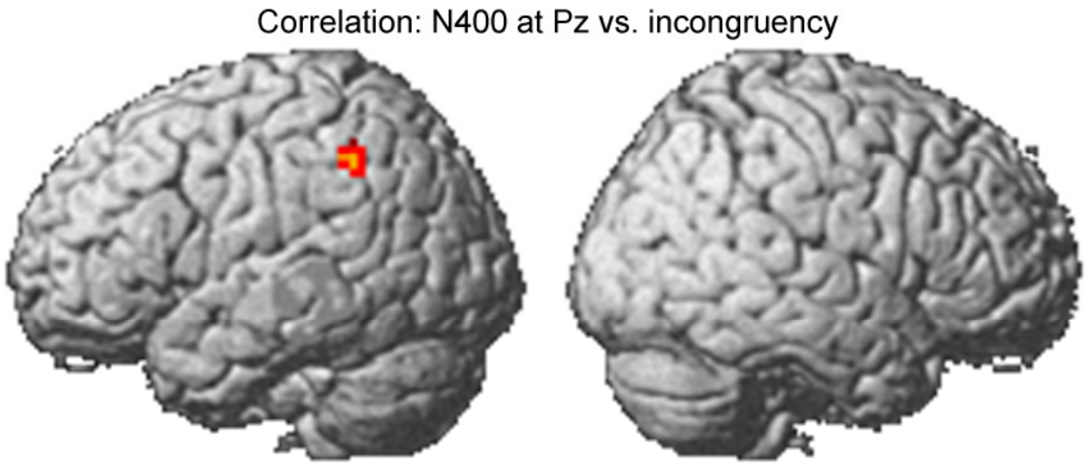
SM Figure 6.2. Incongruency effects: one sample t-tests.
Both the control children (A) and the children with dyslexia (B) showed increased activation for incongruous compared to congruous endings in inferior frontal regions. In addition, the control children also showed increased activation for incongruous than congruous endings in the inferior parietal, the superior temporal and middle occipital regions of the left hemisphere, although only the inferior parietal activation effect was larger than in dyslexic children when compared directly (see manuscript).



SM Figure 6.3. ERP-maps with group differences and selected waveforms in response to incongruous and congruous sentences endings

The ERP maps (A) in response to incongruous and congruous sentence endings show posterior positivities in all 4 microstates indicating that the posterior negativity of the N400 effect results from reduced posterior positivity for the incongruous endings (first 3 rows). Difference t-maps between children with and without dyslexia (4th row) indicate that the reduced N400 effect (N400b; see manuscript) resulted mainly from differences in response

to incongruous endings. Prominent group differences were also found for microstate LPa, but similarly for incongruous and congruous endings.
Waveforms (B) in response to incongruous and congruous sentence endings are shown at 3 midline electrodes (occipital: Oz; parietal: Pz; central: Cz) for the dyslexic (red) and control (black) children. The segments showing incongruency effects based on the map comparison are indicated in grey.



SM Figure 6.4. Correlation between the N400 at Pz and fMRI activation
Adding the N400 amplitude at Pz electrode to the fMRI incongruency model in SPM revealed a significant correlation ($p<0.001$) in the inferior parietal lobule (Talairach coordinates: -50/ -44/ 44) indicating an increasing fMRI incongruency effect with an increasing N400 effect.

7 Reading for meaning in dyslexic and young children: EEG and fMRI evidence for distinct neural pathways but common endpoints

7.1 Introduction

Developmental dyslexia severely impairs affected children and adults in accessing all written information. Behavioural studies indicated that phonological processing deficits lie at the core of dyslexia (Bradley and Bryant, 1978; Ramus et al., 2003; Vellutino et al., 1995), and that semantic impairments may develop later as a consequence of the phonological deficits interfering with basic word recognition (Vellutino et al., 1995). However, behavioural studies alone may not be conclusive about the nature of the semantic processing deficits, as similar behavioural response patterns can arise from very different neural mechanisms.

Here we combine multimodal imaging (Schulz et al., 2008) and comparisons with a younger control group matched for reading level (Hoeft et al., 2006) for a novel neuroimaging approach at specific neural correlates of dyslexia. Probing both semantic processing and basic word recognition the present study extends previous findings on the phonological core problem in dyslexic children (Hoeft et al., 2006; Hoeft et al., 2007) and complements behavioural studies on semantic processing impairments (Chabot et al., 1983; Howell and Manis, 1986; Stanovich et al., 1988; Vellutino et al., 1995).

Only few brain imaging studies on developmental dyslexia have studied higher order language processing such as semantic integration processes during sentence reading. fMRI studies located the semantic impairment in dyslexics to temporoparietal brain regions. In a semantic judgement task (Booth et al., 2007) found a weaker correlation between semantic association strength and brain activation in inferior frontal, middle temporal and inferior parietal regions in dyslexic children compared to controls. Similarly, (Schulz et al., 2008) used a sentence verification task and found reduced inferior parietal activity associated with semantic incongruency in dyslexia, which could be linked to late semantic processing after 320ms through multimodal imaging based on fMRI and EEG (Electroencephalogram). Further studies with no explicit analysis of semantic processing but semantic tasks (e.g. categorisation) found effects of dyslexia in occipitotemporal (Shaywitz et al., 2002), middle temporal and supramarginal/inferior parietal (Kronbichler et al., 2006), and middle temporal and (right hemispheric) inferior parietal regions (Meyler et al., 2007).

Furthermore, Meyler and colleagues (2007) found the left inferior parietal effects of dyslexia to increase with age, indicating a widening gap between good and poor readers with age as suggested by behavioural data (Vellutino et al., 1995).

In a similar vein, ERP (event-related EEG potentials) and MEG (Magneto-encephalography) studies of semantic incongruency effects in sentence reading paradigms found semantic processing to be affected in dyslexia. The main electrophysiological signature of incongruency is termed N400 and is most clearly visible as an N400 effect in the difference ERP between unexpected (incongruous) and expected (congruous) sentence endings (Kutas and Hillyard, 1980). Several studies revealed an affected semantic processing in dyslexia by showing topographically different (Brandeis et al., 1994; Schulz et al., 2008), delayed (Brandeis et al., 1994), and attenuated (Brandeis et al., 1994; Helenius et al., 1999; Schulz et al., 2008) N400 effects. Contrarily, (Neville et al., 1993) even found an enlarged N400 effect for younger (8 to 10 year old) language impaired children compared to controls. Sabisch and colleagues (2006) did not find any semantic N400 differences between dyslexic children and controls in an auditory paradigm. No differences between the N400 effect of dyslexic adults and controls were found by (Robichon et al., 2002), but dyslexic adults showed a prolonged semantic N400 effect for word pairs in another study (Rüsseler et al., 2007). Taken together, deviant semantic processing in dyslexia during the N400 time range seems specific for reading in context but dependent on age and task demands.

Most imaging studies (e.g. (Booth et al., 2007; Kronbichler et al., 2006; Sabisch et al., 2006; Schulz et al., 2008) revealed deviant brain processes in dyslexia by comparing groups matched for age. Unfortunately, these also differ in the amount of reading experience (Bradley and Bryant, 1978). Accordingly, semantic impairments might originate from deficits at an earlier stage of language processing and thus just be a consequence of low reading performance due to basic word recognition and phonological deficits.

For phonological processing deficits, this problem has been addressed in behavioural developmental research (e.g. (Bradley and Bryant, 1978; Goswami et al., 2002; Snowling et al., 2000; Wimmer, 1996) and in two neuroimaging studies (Hoeft et al., 2006; Hoeft et al., 2007) by including an additional control group with younger children who have similar reading abilities as the dyslexic children. Within this design, comparing a dyslexia group (DYS), a group of age-matched, superior readers (CA), and a group of younger, reading level matched children (RL) may separate influences of age, reading ability, dyslexia contributing independently to brain activity during semantic processing and basic word recognition.

A dyslexia-specific semantic processing deficit (similar to the phonological core problem) characterised by a deviant brain development predicts that dyslexic children differ from both age-matched normal readers (Booth et al., 2007; Brandeis et al., 1994; Schulz et al., 2008) and from reading level matched younger children in a similar way. Alternatively, no processing difference between the dyslexic group and the reading level matched younger control group are expected if the semantic deficit is mediated by low reading performance, and is not specific for dyslexia but resembles a developmental delay (Stanovich et al., 1988).

Previous fMRI work suggested that deviant neural processing during phonological tasks was specific for dyslexia, as it also occurred, when dyslexic children were compared to younger, reading level matched controls (Hoeft et al., 2006; Hoeft et al., 2007). As phonological processing contributes to reading words in sentences, we expect for the present study that at least some of the differential effects of such basic word processing during sentence reading that were found in the comparison between the dyslexic children and the 5th grade controls to occur when the dyslexic children are compared to the younger reading-level matched controls.

7.2 Materials and Methods

Subjects

The data of 57 children from 2nd, 3rd, or 5th grade were analysed in this study. According to the matching procedure (supplementary document 1) the children were assigned to one of 3 groups of dyslexic 5th graders (10m/9f), control 5th graders (9m/10f), and control 2nd/3rd graders (16m/3f).

As required by the matching process the 5th graders with dyslexia did not differ from the younger control children with respect to their reading speed (correct words per minute). However, the p-value for this difference was only slightly above 0.1 (see table 7.1), and in order to exclude a potentially confounding effect, we additionally tested whether the critical effects of ANOVA analyses held when the correct word per minute score was added as a covariate to the DYS vs. RL contrasts. Similarly, as there were more boys in the reading-level matched control group compared to the other two groups, we tested whether the critical effects of the ANOVA analyses held when tested with subgroups matched for sex (each 9m/3f; fMRI: 7m/2f). It is reported if a group main effect or an interaction involving the group factor changes from significance ($p<0.05$) to non-significance ($p>0.05$) or vice-versa in any of these analyses.

Table 7.1: subjects

	DYS mean ±SD	CA Mean ±SD	RL mean ±SD	DYS vs. RL	DYS vs. CA	CA vs. RL
Age (y)	11.6(±0.3)	11.3(±0.3)	9(±0.7)	p<0.001	p<0.01	p<0.001
non verbal IQ	12.2(±2.2)	12.4(±2.3)	12.5(±2.5)	p>0.2	p>0.2	p>0.2
verbal IQ	11.1(±3)	12.2(±2.2)	14.1(±3.7)	p<0.01	p>0.1	p<0.1
Correct words per minute	49(±6)	94(±15)	55(±15)	p>0.1	p<0.001	p<0.001
Percent range reading ability	5(±3)	57(±29)	50(±24)	p<0.001	p<0.001	p>0.2

*p<0.05, **p<0.01, ***p<0.001;

The children, all with normal or corrected-to-normal vision, were screened for a history of neurological diseases or psychiatric disorders. Their native language was (Swiss-) German. All children participated in two counterbalanced sessions with EEG and fMRI recordings. Four children of the dyslexia group could not participate in the MR session because of dental braces. Keeping the matching criteria we therefore limited the fMRI group size to 15. Children and their parents gave informed consent, and were compensated with a book voucher of 60 CHF for their participation. The study was approved by the local ethical committee.

Nonverbal and verbal intelligence was assessed using the block design and the similarities subtest of the HAWIK-III intelligence assessment battery (Tewes et al., 2000)

Task

The reading task described in (Schulz et al., 2008) comprised sentences with 56 semantically congruous and 56 incongruous endings ("The sky is blue / fat"), and was presented identically in EEG and fMRI in two counterbalanced sessions. The children were asked to read the sentences silently, and to occasionally press a mouse button with the index or the middle finger if the question 'Yes – No?' appeared after a sentence, prompting a judgement whether the previous sentence was meaningful or not. Forty sentences with congruous endings and 40 sentences with incongruous endings - not followed by a motor response - were used for the ERP and fMRI analyses.

Each word in a sentence was presented in the centre of the screen for 280 ms with an SOA of 570 ms. For the sentences requiring a (delayed) response, an additional 'Yes – No?' screen was presented following the final word after 1080 ms. The sentence SOA (for all sentences) and the duration of the null events were 4700 ms. The assignment of the response buttons to the semantic judgment was counterbalanced across subjects.

fMRI recording and analysis

Whole brain functional imaging data were acquired on a 3T (GE medical systems) scanner using T2*-sensitive ultrafast multi-slice echo planar imaging (EPI) sequences sensitive to blood oxygenation level dependent (BOLD) contrast. The task was presented using MR compatible video goggles.

In an event-related design we recorded 566 volumes (25 axial slices of 4.6 mm with 0.4 mm gap, TR = 1499ms, TE= 40 ms, slice resolution = 3.75 mm x 3.75 mm, 64 x 64 pixel matrix, flip angle 50°). The first 5 volumes were rejected to exclude T1 saturation effects. Particular care was taken to stabilise the children using a vacuum cushion, custom made padding and fixations, so that the head movements of all children were kept below 2° in all rotation axes and below 50% of the voxel size in each direction. To reduce acoustic noise subjects were also provided with earplugs.

Image processing and statistical analyses were carried out using SPM5 (http://www.fil.ion.ucl.ac.uk/spm). We used the standard preprocessing steps including slice-scan-time correction, movement correction, normalisation to the Montreal Neurological Institute (MNI) template, and smoothing with a Gaussian kernel of 9 mm.

For statistical analysis the data were high pass filtered with a cut-off of 128 s. We focussed on the semantic incongruency effect comparing incongruous and congruous sentence endings. The stimulation paradigm was modelled with the 4th word of every sentence as a single event convolved with the spm5 implemented hemodynamic response function. Incongruous (n=40) and congruous (n=40) sentence endings which did not require a response were modelled separately. Conversely, sentence endings (n=32) which required a response were modelled separately but excluded from further statistical analysis. Hence, the first 3 words of every sentence, the null events and the response screens were not modelled and served as baseline.

For the group analyses we conducted the SPM5 implemented standard whole brain second level random effects analysis. We computed one-sample t-tests to reveal the additional activations while processing incongruous sentence endings compared to congruous sentence endings (incongruency effect). The more basic word processing mechanisms were computed as the activation during reading of entire sentences starting at the onset of the first word of every sentence with the duration of 2.25s versus baseline. The effects of dyslexia and the developmental effects were assessed by computing three group comparisons with two sample t-tests (CA vs. DYS, RL vs. DYS, CA vs. RL).

The group differences were analysed in more detail with a region of interest (ROI) analysis on unsmoothed data. The ROIs for the incongruency effect, were defined by local maxima of the CA vs. DYS comparison, and are reported in Talairach coordinates (Talairach and Tournoux, 1988). The ROIs for basic word processing were defined by local maxima in the inferior parietal region of the CA vs. DYS contrast for sentence reading. All ROIs had a radius of 9mm.

Using the extracted percent of signal change values (MarsBar software; version 0.41; (Brett et al., 2002) we computed multivariate ANOVAs with the within subject factor “incongruency” (incongruous vs. congruous sentence endings) and the between subject factor “group” (CA vs. DYS, RL vs. DYS, CA vs. RL) and t-tests for the sentence reading contrast.

ERP recording and analysis:

The EEG was recorded using an electrode cap (FMS, Munich, Germany). The children were seated in an electrically shielded, sound proof and air-conditioned room in front of a computer screen 1.2m away. This sentence reading task was part of an ERP test battery presented in a pseudo randomised order. The entire ERP session lasted about 3 hours.

The electrode montage included 64 electrodes consisting of all 10-20 system electrodes and the additional electrodes Fpz, FCz, CPz, POz, Oz, Iz, AF1/2, F5/6, FC1/2/3/4/5/6, FT7/8/9/10, C1/2/5/6, CP1/2/3/4/5, TP7/8/9/10, P5/6, PO1/2/9/10, OI1/2 plus two electrodes below the outer canthus of each eye. The electrodes O1/2 and Fp1/2 were placed 5% more laterally for more even coverage indicated by an apostrophe in the label (e.g. O1').

The EEG was referenced to the Fz electrode, grounded at AFz, sampled at 500 Hz/channel, bandpass-filtered between 0.1 and 70 Hz and calibrated to technical zero baseline. The impedance was kept below 20 kΩ (Ferree et al., 2000).

The ERPs were standard processed in Vision Analyzer software (Brain Products GmbH) including downsampling to 256 Hz, digitally low pass filtering with a 30 Hz filter, correcting for horizontal and vertical eye movements using an independent component analysis (Jung et al., 2000), and transforming to the average reference (Lehmann et al., 1980). Trials with artefacts exceeding ±100 µV in any channel (1 child ±120 µV) were automatically rejected. Before averaging the remaining trials were epoched 125 ms prior and 1125 ms following the stimulus.

ERPs were computed for those incongruous and congruous sentence endings that did not require a response. Difference waves were computed by subtracting the congruent ERP from the incongruent ERP. ERPs were also computed in response to all 448 presented words. Grand averages were computed from the incongruous minus congruous difference ERP and from the ERP in response to all words.

In parallel to the voxel-based analysis of the fMRI data, we analysed the ERP by computing a time-point-wise Topographic Analysis of Variance (running TANOVA) on raw ERP maps (unnormalised). A TANOVA on raw maps detects all systematic amplitude differences between two maps by computing a nonparametric randomisation test on the GFP of difference maps (Schulz et al., 2008; Strik et al., 1998).

First, we computed a running TANOVA of the incongruency effect across all 57 children comparing ERP maps of incongruous endings to those of congruous endings ($p<0.01$).

Second, we computed running TANOVAs for each of the three group comparisons (CA vs. DYS, RL vs. DYS, CA vs. RL) on the ERP in response to the incongruency effect and on the ERP in response to all words) To detect even subtle differences and partial replications, we lowered the statistical threshold for the group comparisons to trend level ($p<0.1$). We further computed statistical t-maps for all three group comparisons in time windows significantly different in the comparison between the 5th grade groups.

In order to test for differences in latency and map strength for the incongruency effect between dyslexic children and controls we applied a Topographic Component Recognition (TCR / (Brandeis et al., 1992; Brem et al., 2005). For TCR analysis a template map from the grandaverage of all 57 children was used to search for the topographically most similar map in each individual ERP. For the incongruency effect we concentrated on the N400 effect and took as a template the map occurring at the GFP peak. For basic word processing we selected the P1, N1, and P2 segments defined by GFP minima as topographic template (as in (Schulz et al., 2008).

In order to avoid a topographical match with noise the incongruency data were low-pass filtered (5 Hz) and - for all data - time points with high GFP (i.e. low noise) were favoured by adding 5% GFP to the correlation (Brem et al., 2005; Steger et al., 2000). The latencies and GFP values of the time points with the highest correlations were chosen for the group comparisons (t-tests).

As supplementary illustration (Supplementary Figure 7.1 and 7.2) we created series of maps at regular intervals depicting each group's grand averages of the difference ERP (incongruous minus congruous) and of the ERP to all words, together with the corresponding group comparisons (t-maps).

Behavioural analysis

We computed three multivariate ANOVAs with the within-subject factor "incongruency" (incongruous vs. congruous sentence endings) and "modality" (EEG vs. fMRI), and the between-subject factor "group" (CA vs. DYS, RL vs. DYS, CA vs. RL) separately for accuracy and response speed. The incongruous condition was composed of responses to both incongruous colour and incongruous non-colour endings, the congruous condition of responses to both congruous colour and congruous non-colour endings.

7.3 Results

7.3.1 Behavioural data

The analysis of the behavioural data (Supplementary Material table 7.1) revealed a significant main effect of incongruency (incongruent vs. congruent sentence endings) for response time but not for accuracy (percentage of correct responses) in all 3 group comparisons, due to increased reaction time for incongruous compared to congruous sentence endings (all 3: $p<0.01$; in sex matched comparison for RL vs. DYS and CA v.s DYS: $p<0.1$). No main effect was found for modality (EEG/fMRI). The 5th grade control children responded faster and more accurately than 5th grade dyslexics (both $p<0.001$) and 2nd/3rd graders (reaction time: $p<0.001$; accuracy: $p<0.01$). There were no differences between the dyslexic and the reading level matched groups neither for accuracy nor for response time (both $F<1$). The only additional significant effect in these analyses was an interaction between modality and incongruency for accuracy ($p<0.05$) in the MANOVA that included the dyslexic children and the age matched control group, reflecting a larger incongruency effect (more accurate for incongruous than congruous endings) for the fMRI compared to the ERP session.

After reduction of the group size to equal the contribution of both sexes an additional interaction effect modality x incongruency x group ($p<0.01$) became significant in the CA vs. RL contrast for reaction time, indicating a larger incongruency effect for the younger compared to the older control children in the EEG session, as opposed to a larger incongruency effect for the older compared to the younger children in the fMRI session.

7.3.2 fMRI results

Semantic processing during sentence reading

Voxel-based analyses

All children. The analysis of the incongruency effect across all children revealed increased activation in inferior frontal and middle temporal areas of the left hemisphere for incongruous compared to congruous endings ($p<0.001$ uncorrected, Figure 7.1A; Supplementary Table 7.2). More activation for congruous than incongruous sentence endings was found bilaterally in the precuneus, the cingulate cortex, the inferior parietal lobule, and the middle frontal gyrus and furthermore in the left hemispheric superior parietal lobule as well as in the right hemispheric superior frontal gyrus ($p<0.001$, uncorrected; Figure 7.1A; Supplementary Table 7.2).

Group contrasts. Dyslexic 5th graders showed a reduced incongruency effect in the inferior parietal lobule compared to the 5th grade control group with two local maxima ($p<0.005$, uncorrected; Figure 7.1; Table 7.2). In the same region the younger control group showed also a reduced incongruency effect compared to the older control group, whereas they did not differ from the children with dyslexia using the same statistical threshold.

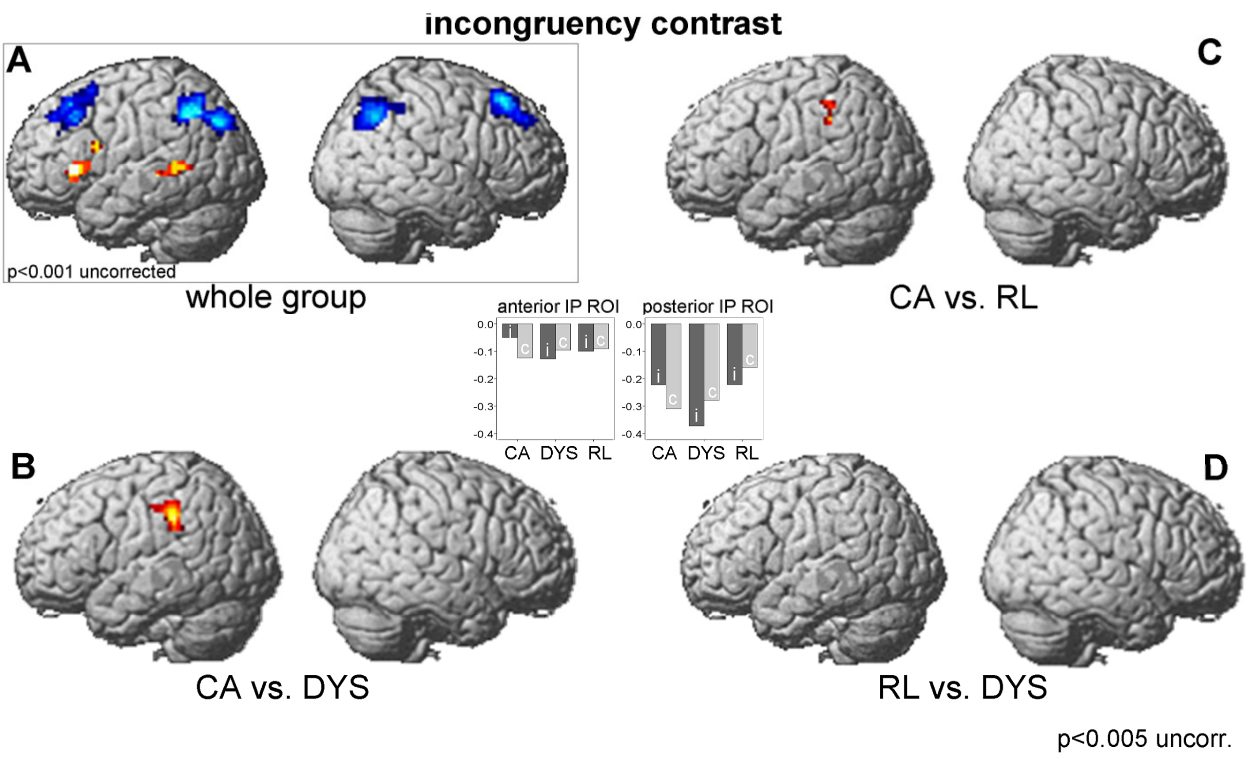


Figure 7.1. Incongruency fMRI effects. Across all children incongruous endings elicit larger activation than congruous endings in left inferior frontal and middle temporal regions (warm colors), while congruous endings elicit larger activation in bilateral inferior parietal and superior frontal regions (A). Whereas 5th grade control children show a larger incongruency effect compared to dyslexic children (B) and compared to younger control children (C) in the left inferior parietal region, no differential incongruency effect is found between children with dyslexia and the younger control children (D). These differential incongruency effects modulate an overall deactivation in the inferior parietal region (IP ROIs; bar graphs).

ROI analyses

CA vs. DYS. For both ROIs there were significant “incongruency x group” interaction effects (anterior: $p<0.01$ / $p<0.1$ with sex-matched groups; posterior: $p<0.001$; see F-values in Supplementary Table 7.4), reflecting a differential effect on percent signal change in response to incongruous endings in the two groups with reduced deactivation in CA and increased deactivation in DYS compared to the congruous endings (see also Figure 7.1).

RL vs. DYS. The “incongruency x group” interaction clearly missed significance (both $F<1$). In the posterior ROI there were main effects for both “incongruency” ($p<0.001$) and “group” ($p<0.05$ / $p<0.1$ with sex-matched groups) reflecting increased deactivation for incongruous than congruous endings across both groups, and increased deactivation in the DYS compared to the RL group across both types of endings.

CA vs. RL. “Incongruency x group” interactions for both ROIs (both $p<0.01$ / anterior with sex-matched groups: $p<0.1$) were found, also reflecting the reduced deactivation for incongruous compared to congruous endings in the CA group, and similar or even larger deactivation for incongruous compared to congruous endings in the RL group (see also Figure 7.1). This interaction also modulated the “incongruency” main effect in the anterior ROI ($p<0.05$).

Basic word processing during sentence reading

Voxel-based analyses

All children: The whole group of children activated a predominantly left-lateralised language network during sentence reading (Figure 7.2A) including inferior occipito-temporal, middle temporal, and inferior frontal areas.

Group contrasts. In the voxel-based group analyses of the sentence reading contrast (vs. rest) we found decreased brain activation for children with dyslexia compared to age-matched controls mainly in the left inferior parietal region (all $p<0.001$ uncorrected, Figure 7.2; Table 7.3). Additional activation decrease was found in the left hemisphere in medial and superior frontal areas, and in the fusiform gyrus. No regions were found with increased activation in children with dyslexia compared to controls.

Compared to the reading-level matched controls the children with dyslexia showed decreased activation in similar (though bilateral) inferior parietal and medial/superior frontal areas. Additional activation decrease was found in middle temporal areas of the left hemisphere and in the cingulate region. No regions were found with increased activation in children with dyslexia compared to controls.

No activation differences associated with sentence reading were found between the older and younger control groups.

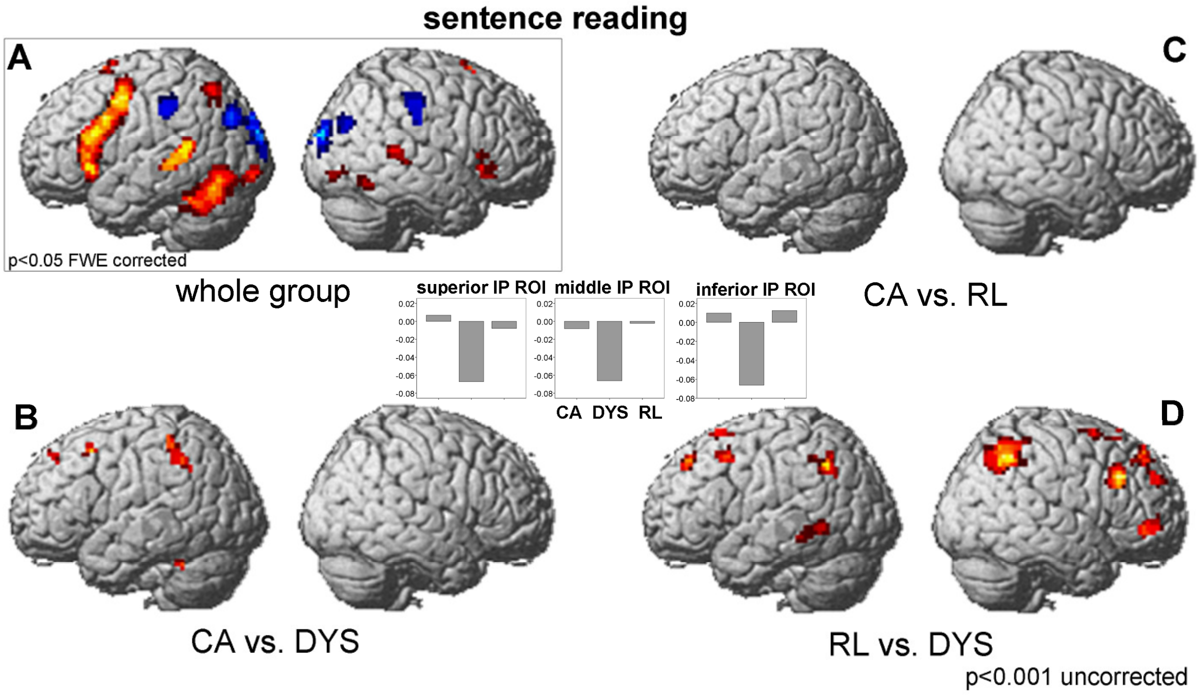


Figure 7.2. Sentence reading fMRI effects. Reading sentences activated a predominantely left-lateralised language network across all children including inferior frontal, middle/superior temporal, and inferior occipito-temporal regions (A). Dyslexic children show reduced activation compared to age-matched controls (B), but also compared to reading-level matched controls in the left inferior parietal region (D), whereas the two control groups did not differ (C). Deactivation in the dyslexic children was found similarly in three inferior-parietal (IP) ROIs based on the CA vs. DYS contrast (bar graphs).

ROI analyses

CA vs. DYS. Children with dyslexia differed from 5th grade controls in all 3 ROIs (superior/middle: $p<0.001$; inferior: $p<0.01$) mainly due to an increased deactivation in the children with dyslexia (compare Figure 6. 2).

RL vs. DYS. Children with dyslexia differed in a similar way from the younger control group in all 3 ROIs (superior: $p<0.1$ / $p<0.05$ with sex-matched groups; middle: $p<0.01$; inferior: $p<0.05$).

CA vs. RL. No differences were found between the two control groups in any of the 3 ROIs (all t-values between -1 and +1).

Table 7.2. Results of voxel-based between-group comparison for the incongruency contrast

Cluster size	t	x	y	Z	Location	BA
Incongruency effect: age matched groups (CA vs. DYS)						
100	3.46	-59	-30	43	Inferior Parietal Lobule	40
	3.15	-59	-39	30	Inferior Parietal Lobule	40
Incongruency effect: control groups: (CA vs. RL)						
36	3.71	-56	-36	46	Inferior Parietal Lobule	40
	3.21	-59	-27	43	Inferior Parietal Lobule	40
14	3.41	-59	-39	32	Inferior Parietal Lobule	40

7.3.3 ERP results

Semantic processing during sentence reading

Time-point-to-time-point analysis

All children: Incongruous sentence endings were processed differently ($p<0.01$; see Supplementary Figure 7.2A) from 285 to 577 ms (N400 effect) and from 652 to 1125 ms (late positivity, LP).

Group contrasts. The incongruency effects within the N400 range differed ($p<0.1$) between the 5th grade control group and the 5th grade dyslexics (301 – 397 ms), as well as between the 5th grade control group and the 2nd/3rd grade control group (277 - 405 ms). Similar to the fMRI incongruency results we found no differences in the N400 time range between the children with dyslexia and the reading level matched younger group. Although they differed briefly during an early time range (230 to 265 ms), this difference occurred before the start of robust incongruency effects in all children at 285 ms.

Additional group effects occurred after the N400 range in all group comparisons, but were only short-lasting. We therefore focussed on the robust N400 group effects in the further analyses. Illustrations of the other findings can be found in the map series across the entire time range in the Supplementary Material (Supplementary Figure 7.1).

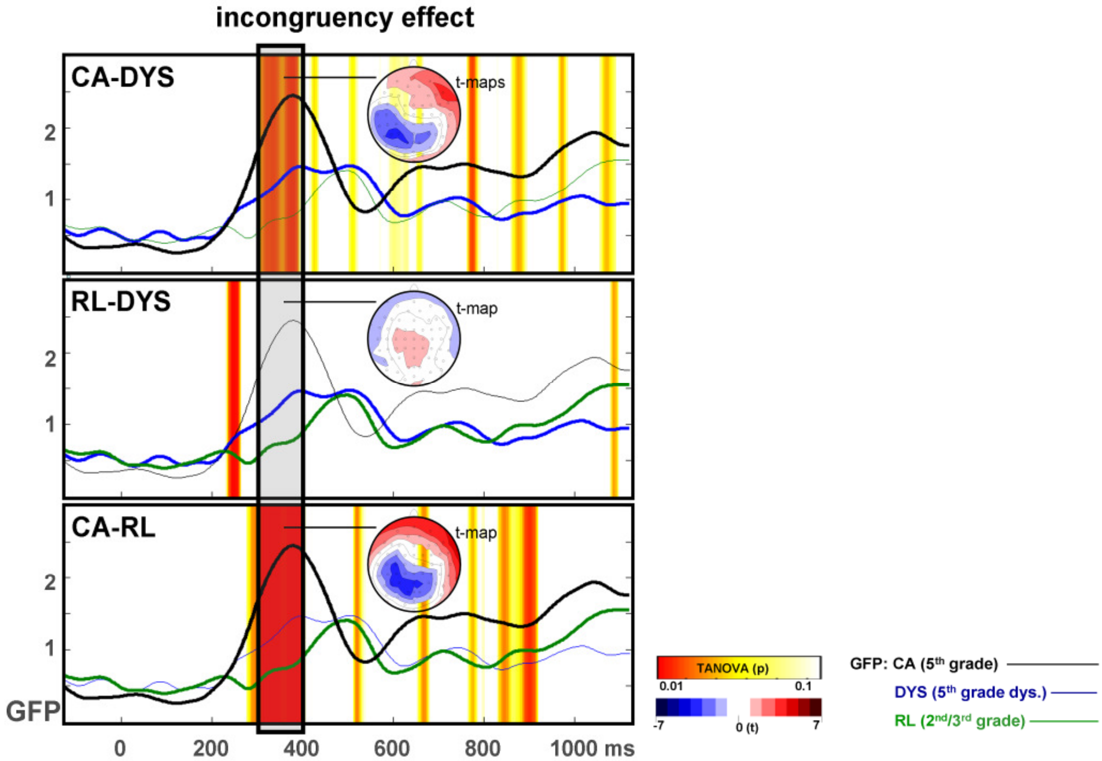


Figure 7.3. Time-point-wise ERP incongruency effects. The incongruency effect differs in 5th grade control children mainly between 301 and 397 ms compared to children with dyslexia and between 277 and 405 ms compared to the younger control children as indicated by the colour-coded TANOVA results. These differences encompass the GFP peak of the difference ERP (incongruous minus congruous) in the 5th grade control children, which is more prominent than in the other two groups (waveforms). The t-maps of these group differences in the N400 time range (301 and 397 ms) show similar topographies with left posterior negativity and right anterior positivity. Dyslexic children's incongruency effect during the same time range does not differ from reading-level matched control children. They differ, however, during an earlier time range, before robust incongruency effects occur across the whole group (<285 ms).

N400-effect analyses

Map latencies and GFP: Group comparisons revealed a delayed N400-effect for the DYS group ($p<0.05$) as well as for the RL group the ($p<0.001$), both compared to the normally reading 5th graders. We found no differences between the reading level matched groups ($p>0.2$; Supplementary Table 7.6). There were also no group differences of GFP at the individual N400 latency as determined by the TCR procedure in any of the 3 group contrasts (all $p>0.2$).

Statistical t-maps: Analogous to the fMRI ROI analysis we chose the time window with the group differences in the N400-effect from the CA vs. DYS contrast as a time window of interest (301 - 397 ms). Voltage maps averaged across this time window were used for group contrasts (CA vs. DYS, RL vs. DYS, CA vs. RL) in statistical t-maps.

As indicated by the t-map topographies (Figure 7.3), the older control group showed a similar topography of the N400-effect increase compared to the children with dyslexia (21 electrodes larger than t=2), as compared to the younger control group (28 electrodes larger than t=2). No robust differences occurred in the t-map of the contrast between children with dyslexia and the younger control group (no electrode larger than t=2)

Basic word processing during sentence reading

All children. The ERP in response to all words in a sentence mainly revealed three microstates, corresponding to the P1, N1, and P2 components (see Supplementary Figure 7.2B).

Group contrasts. Applying TANOVA analyses processing of the words differed between children with dyslexia and age-matched controls during three time windows: at trend level within the P1 microstate (98 – 128 ms) and in later sections after the N1 (375 - 413 ms and 453 - 495 ms). Processing differences during the P1 microstate were found between the children with dyslexia and the reading level matched control group in a time window between 94 - 159 ms. The same comparison also revealed pronounced differences in the N1 time range (215 - 300 ms) and at the P2 offset (402 - 429 ms). Comparing the older and younger control groups also revealed processing differences in the N1 time range (207 - 308 ms) including a brief difference at the P1/N1 transition (145 - 171 ms), probably reflecting developmental effects in the N1 component and within a small time window (363 – 378 ms) remaining at trend level during the offset of the P2.

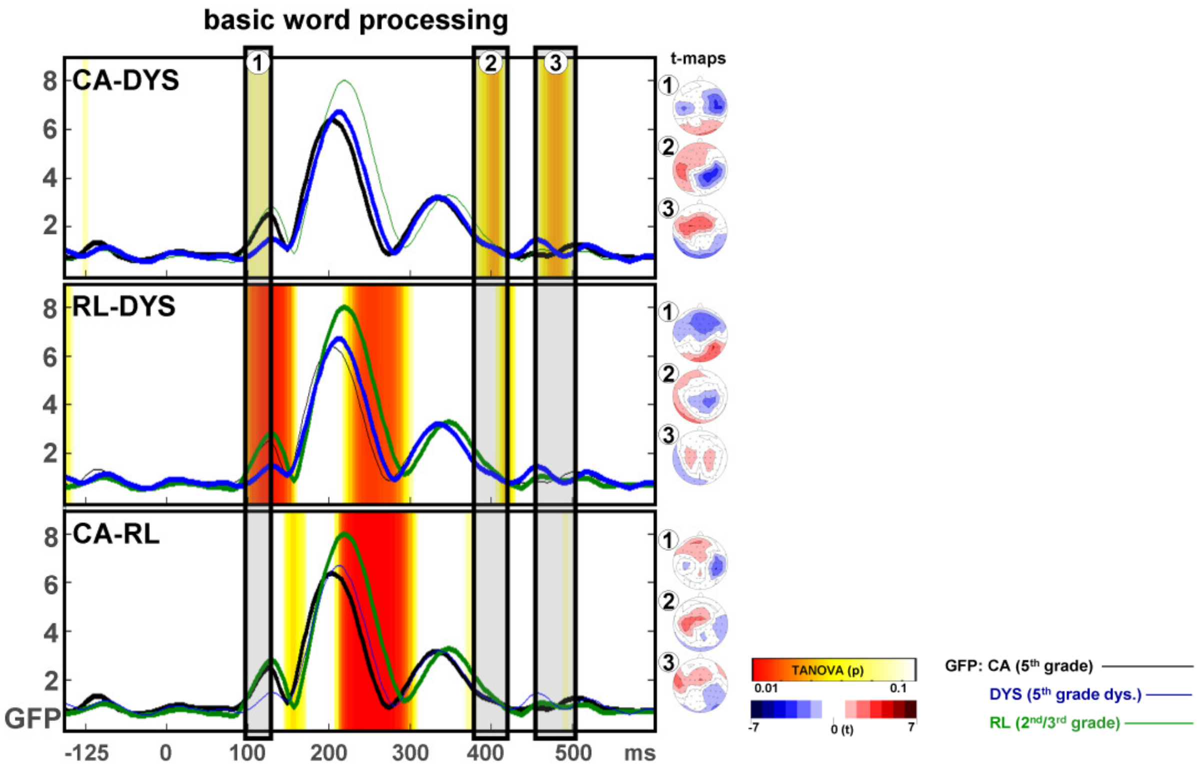


Figure 7.4. Time-point-wise basic ERP sentence reading effects. The TANOVA results of the CA vs. DYS contrast reveal differences at the trend level in the P1 component (GFP peak around 100 ms) that also occur in the DYS vs. RL contrast with partially overlapping topographies in the t-maps (right side). Additional differences after 350 ms occurred mainly in the CA vs. DYS contrast, but only for a few time points or at the trend level in the other two contrasts. Prominent group differences in the TANOVA occurred between the younger control children and each of the other two groups during the N1 (GFP peak around 200 ms) offset, reflecting developmental effects.

Latency and GFP. Children with dyslexia differed in basic word processing from age-matched controls in a latency delay of their N1 component ($p<0.05$, Supplementary Table 7.6). The longest N1 latencies, however, were found in the younger control group, which lead to a significant delay compared to both other groups (RL vs. CA: $p<0.001$; RL vs. DYS: $p<0.05$, for the sex matched groups at trend level: $p<0.1$), also reflected in a delay of the subsequent P2 component (RL vs. CA: $p<0.01$; RL vs. DYS: $p<0.05$, for the sex matched groups at trend level: $p<0.1$). No group effects were found for the P1 latency (all $p<0.2$).

No significant GFP effects were found in the three group comparisons, but trends ($p<0.1$) towards a larger N1 in the younger control children compared to both other older groups, reaching significance for the sex matched comparison of the RL vs. DYS contrast.

Statistical t-maps. As in the group comparisons for incongruency we were choosing Time Windows of Interest based on the CA vs. DYS TANOVA contrast for basic word processing ($p<0.1$). Voltage maps averaged across the three time windows (P1: 98 - 128 ms; P2-offset: 375 - 413 ms, post P2: 453 – 495 ms) were used for group contrasts (CA vs. DYS, RL vs. DYS, CA vs. RL) in statistical t-maps.

In the P1 segment the t-maps confirmed significant differences for the RL vs. DYS contrast. Both the CA vs. DYS and the CA vs. RL contrast revealed focal differences at frontal and right-temporal electrodes, plus small effects at two occipital electrodes, consistent with attenuated P1 aspects in the DYS group.

In the remaining two segments appreciable differences were found only for the CA vs. DYS contrast at right centroparietal electrodes (during the P2-offset) and frontocentral electrodes (post P2).

7.4 Discussion

In the present multimodal study we examined, whether neural markers of impaired semantic processing and of impaired basic sentence reading and word recognition in dyslexia are related to a deviant brain development and are, hence, specific for dyslexia, or whether they are rather related to general impairments in reading performance and resemble a developmental delay. The approach to study dyslexic children using an additional reading level matched, younger control group is novel to neuroimaging (Hoeft et al., 2006; Hoeft et al., 2007).

By using a subset of control children with lower average reading skills we were able to replicate our recent study about the semantic processing impairment in dyslexia (see Suppl. Material). We found reduced incongruency effects for children with dyslexia in a left inferior parietal region as revealed by the fMRI data and around 400 ms (N400 effect) after presentation of the sentence ending as revealed by the ERP data both indicating impaired semantic processing. This replication suggests that the semantic dyslexia effects published previously also held with a control group restricted to intermediate readers, as the excellent readers were excluded from the present study.

Our findings are in line with those studies suggesting a specific semantic impairment in inferior parietal regions in dyslexia (Schulz et al., 2008); (Booth et al., 2007). Furthermore, we confirmed fMRI studies that included a semantic task but no specific semantic analysis reporting a similar reduced activation in dyslexics (Kronbichler et al., 2006; Meyler et al., 2007).

The reduced and delayed N400 effect corroborates results from previous neurophysiologic studies on semantic processing in dyslexia (Brandeis et al., 1994; Helenius et al., 1999), although some other studies found only prolonged N400 effects (Rüsseler et al., 2007), or different effects of dyslexia in younger children (Neville et al., 1993), or in adults using a slower presentation rate (Robichon et al., 2002).

Establishing the presence of the main neural markers of semantic impairment from our previous report allowed us to address the main question of the present study: Are these markers dyslexia-specific or do they rather resemble a developmental delay?

The younger control group showed a similarly reduced fMRI incongruency effect in the inferior parietal cortex and a similarly reduced N400-effect compared to the older control group, indicating a developmental effect. When the younger control children were compared to the dyslexic children no such difference occurred, also arguing against a dyslexia-specific impairment.

As in our previous report (Schulz et al., 2008) the ROI analysis in the left inferior parietal region showed an overall deactivation of the sentence ending relative to baseline. The ROI analysis also corroborated the voxel-based full brain analysis by showing group-dependent modulation of the deactivation by the incongruency status of the sentence ending. Incongruous endings led to a reduction of the deactivation compared to congruous endings in the older control children, but to an increased deactivation in both the children with dyslexia and in the younger control children. Notably, the ROI analysis also failed to find significantly different incongruency modulation between the children with dyslexia and the younger control group, suggesting similar semantic modulation effects in the groups.

We have argued previously (Schulz et al., 2008) that the incongruency modulation of the overall deactivation may reflect an active semantic process that co-occurs with a process that is active during baseline and responsible for the overall deactivation. The group-specific modulation in the present results may suggest that better readers apply more semantic resources to make sense of incongruous sentence endings, whereas younger children and children with dyslexia use those resources rather to process congruous endings.

The t-maps of the N400 effect confirmed the time-point-wise analysis and further demonstrated that the differences between children with dyslexia and age-matched controls on one side and the differences between the younger and the older control children on the other side showed similar topographies suggesting similar differences at the neural processing level. The latency analysis suggests that at least part of the reduced N400 effect is due to its longer latency in younger children and in children with dyslexia. Delayed N400 effects in dyslexia have been reported previously (Brandeis et al., 1994; Helenius et al., 1999). Latency effects, however, seem to be susceptible to noise, as we could find latency effects only with additionally filtered data in the present study eliminating high-frequency “noise”, but not in our previous report using standard filter settings (Schulz et al., 2008).

For basic sentence reading, we first corroborated our previous results (Schulz et al., 2008). As in the semantic analyses a reduced activation in the inferior parietal region and additionally in frontal regions for basic word processing during sentence reading in the fMRI data of the dyslexic children compared to the age-matched control group was found. The corresponding reduction of the P1 component in the ERP data (Schulz et al., 2008), however, was only significant at a trend level within the TANOVA analysis.

Addressing again the question of dyslexia specificity for basic word processing, the dyslexic children showed reduced activation in similar left and additional right inferior parietal and frontal regions for the sentence reading contrast compared to the reading level matched younger control group. The absence of any difference in the comparison between the younger and the older control groups also suggests the absence of any major developmental effects in this region. Suggesting a dyslexia-specific impairment in basic visual word processing, the ROI analysis corroborated the voxel-based results and revealed a dyslexia specific increased deactivation in the left inferior parietal region.

Despite phonological processing was more implicit in the present semantic congruency judgement task, the finding resembled closely the findings of (Hoeft et al., 2006), which applied an explicit phonological task. The reduced inferior parietal activation thus may reflect a (explicit and implicit) phonological processing deficit, although neither our study (sentence reading vs. rest) nor the study by Hoeft et al.

(rhyming vs. rest) included a specific phonological contrast controlling for more basic word recognition effects.

We could not replicate a robust P1 reduction in the present sample which may be due to the exclusion of the excellent readers in the present sample. However, a trend for a P1 reduction was present for the dyslexic children but not for the younger children suggesting a specific rather than a developmental effect. The t-maps at around 100ms confirm that this reduction reached significance in both contrasts involving the dyslexic children at a number of frontal and right-temporal electrodes. The most prominent group effects in the ERP data of the basic word processing analysis reflected developmental differences in the N1 component with longer latencies in the younger children compared to both other groups. The N1, however, was also delayed in the children with dyslexia compared to the age-matched controls, suggesting that this effect resembles rather a developmental delay.

The behavioural results paralleled the results of the semantic analyses showing similar advantages (higher accuracy and faster reaction time) for the older control children compared to the children with dyslexia as when compared to the younger control children. The absence of group differences for the incongruency effect suggests that the semantic impairment at the neural level affected the behavioural responses similarly for congruous as for incongruous sentence endings.

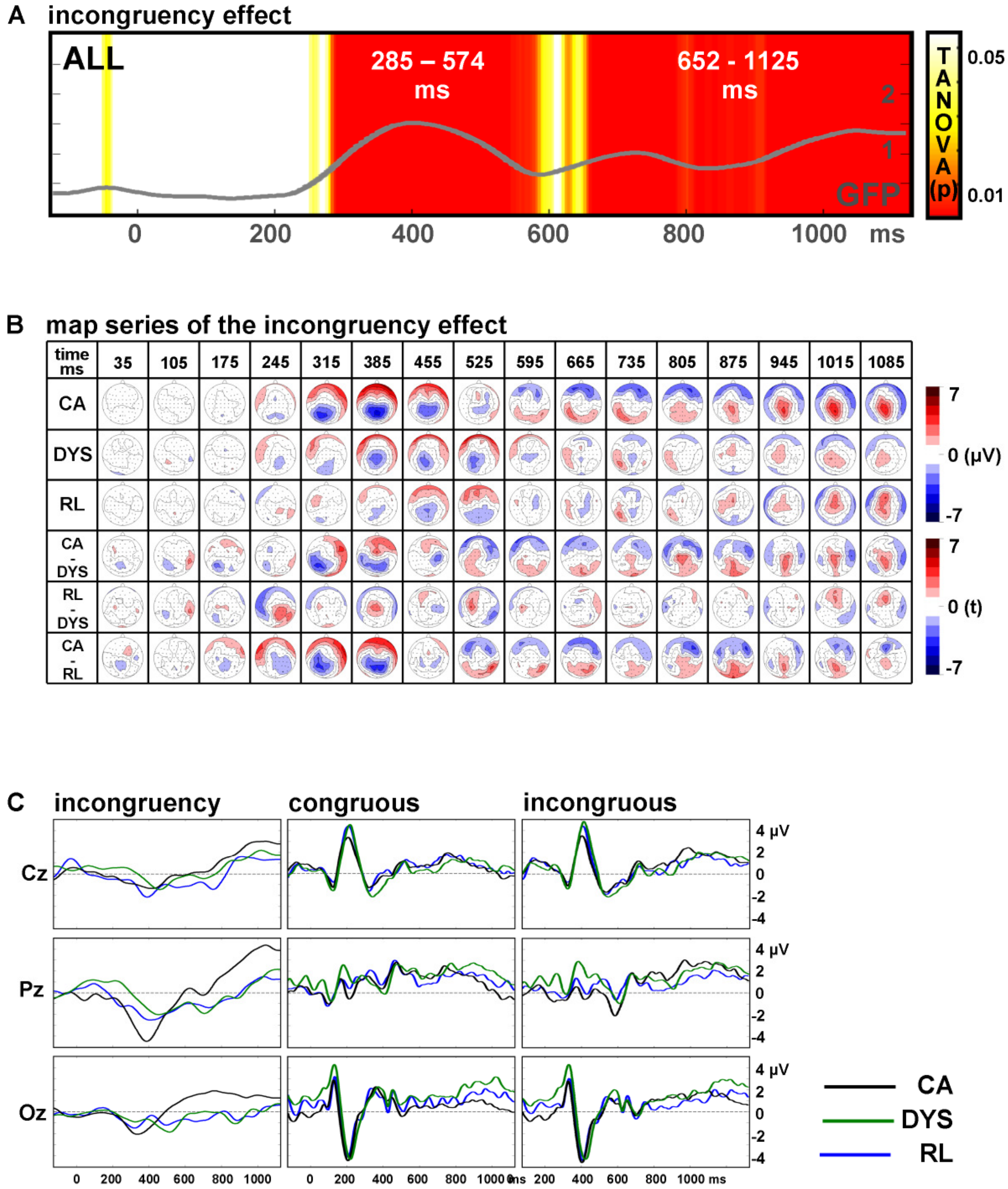
Overall, the different result patterns for basic and for semantic processing impairments in the comparison between children with dyslexia and reading-level matched controls suggest a differential role of these neural markers of dyslexia. Basic sentence reading deficits do not just reflect the low reading abilities due to dyslexia, but reflect qualitatively different brain functions.

Semantic impairments during sentence reading instead appear to follow from the phonological/basic word recognition deficits mediated by low reading ability, in agreement with behavioural results (Vellutino et al., 1995). These semantic processing changes are not dyslexia-specific suggesting the resemblance of a developmental delay. They characterise a low level of reading ability irrespective of whether the cause is young age or a deficit in basic visual word recognition.

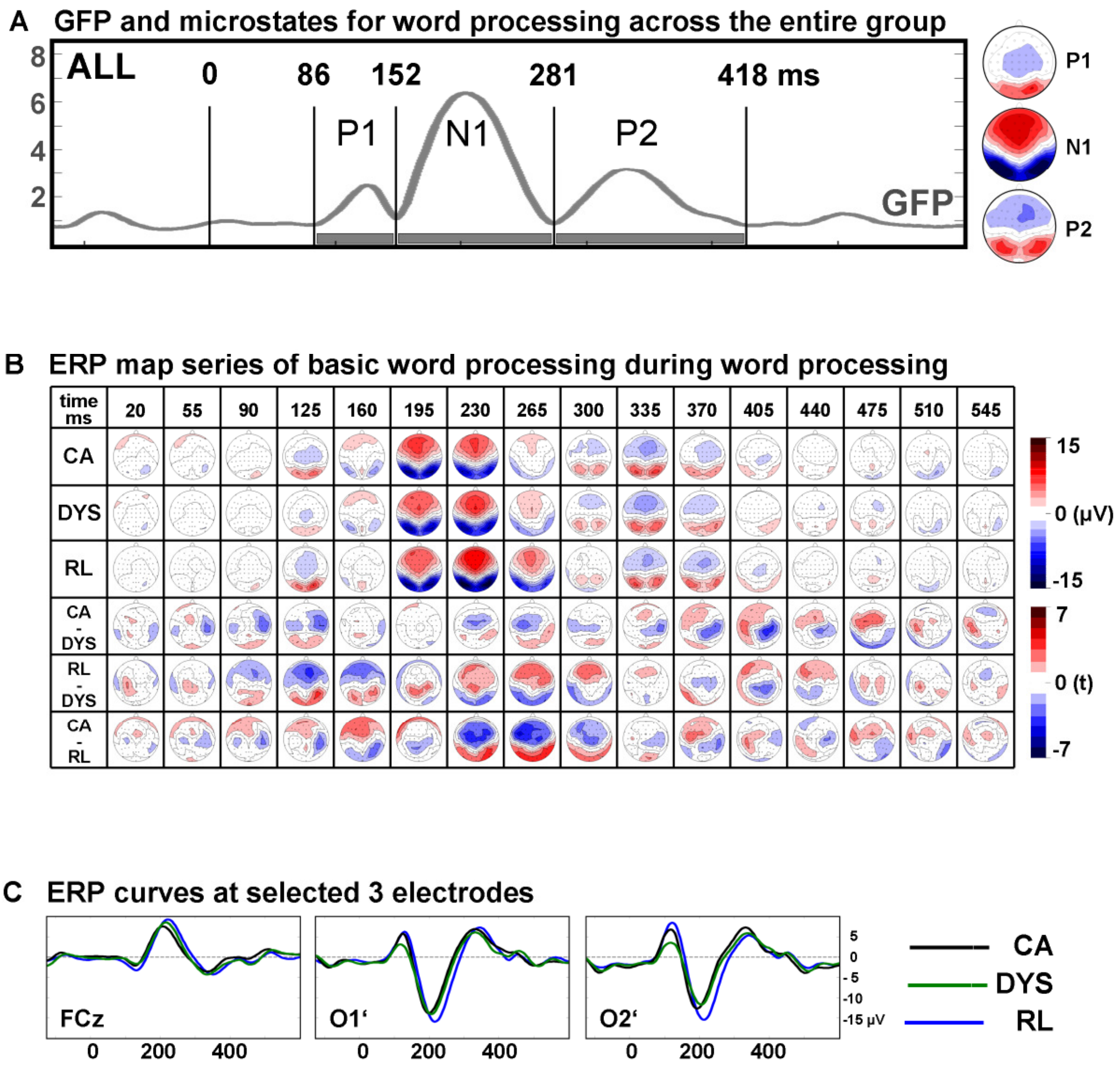
7.5 Acknowledgements

This research was supported by the SNSF grant 32-108130 and the EU FP6 program NeuroDys.

7.6 Supplementary Material



Supplementary Figure 7.1. TANOVA and Global Filed Power (GFP) for the incongruency effect across the entire group (A), continuous ERP segment map series for the incongruency effect (B) and the ERP curves at 3 selected electrodes in response to congruous and incongruous endings and for the incongruency effect for all three experimental groups (C). The upper 3 rows in (B) show the maps for each experimental group and the lower 3 row show the t-maps for all group comparisons in averaged intervals of 70 ms around the indicated time points.



Supplementary Figure 7.2. Global Filed Power (GFP) and microstates of the ERP in response to all words across the entire group (A), continuous ERP segment map series for basic word processing (B) and the ERP curves at 3 selected electrodes in response to words for all three experimental groups (C). The upper 3 rows in (B) show the maps for each experimental group and the lower 3 row show the t-maps for all group comparisons in averaged intervals of 35ms around the indicated time points.

Supplementary document 1: Matching procedure

The novel approach used in this study required to carefully match the reading skills of the younger control children to those of the dyslexic 5th grade children by selection in both groups, and in turn to select a subset of our original group of 5th grade controls (Schulz et al.) to match the relative reading abilities of these younger control children. As a result the 5th grade control children in the present study had peers suffering from dyslexia than in our previous paper.

The 5th grade children were grouped in children with and without dyslexia according to their reading score which was measured using the “Ein-Minuten Leseflüssigkeitstest” (one-minute reading fluency test; (Willburger and Landerl). This test requires the children to read correctly from a list as many words as possible within 1 minute. The resulting “correct words per minute” score of the 5th grade children were compared to the distribution in a normative group of 56 children (Schulz et al.). Children were classified as dyslexic if their “correct words per minute score” was below 10% of the norms (<61.6), and as controls if their score was equal to or above 20% (>=75.0). From our pool of 65 5th grade children we classified 24 children as dyslexic.

The control group of 2nd and 3rd grade children were chosen from a pool of 23 children (18 only with fMRI testing) who also joined our study. We assigned to every dyslexic 5th grade child a non-dyslexic younger child with similar reading ability (i.e. a similar “correct words per minute score in the one-minute reading fluency test) to match the group size as well as the reading skills of the 5th grade dyslexic group. Our control group of normally reading 5th graders was chosen out of 41 normally reading children (30 only with fMRI testing). We assigned every 2nd/3rd grade child a percent rank matched 5th grade child assign according to their grade norms for the “correct words per minute” score (“Salzburger Lesetest”, SLT for the 2nd/3rd graders (Landerl et al., 1997b); one minute reading fluency for the 5th graders, see above). From the 38 chosen 5th graders (dyslexic and controls) 31 5th grade children were part of our longitudinal study (Maurer, 2003; Maurer et al., 2007) 7 children (5 dyslexics) participated only in 5th grade.

Table 7.1. Results of behavioural analysis.

ANOVA F(1,28)	CA vs. DYS		CA vs. RL		RL vs. DYS	
	ACC	RT	ACC	RT	ACC	RT
group	15.26***	16.18***	13.71***	12.45**	<1	<1
modality	<1	1.67	1.8	<1	<1	<1
Incongruency	2.39	9.36**	1.67	9.39**	1.89	10.8**
incongruency*group	<1	<1	<1	<1	<1	<1
modality*group	2.95^{+}	<1	<1	<1	3.21^{+}	<1
modality*incongruency	4.33*	<1	<1	<1	<1	2.11
modality*incongruency*group	<1	<1	<1	<1	<1	<1

p-values (1,28) ($^{+}$: p<0.1, *: p<0.05, **: p<0.01, ***: p<0.001)

Table 7.2. Results of voxel-based incongruency effects across all children.

Cluster size	t	x	y	Z	Location	BA
Incongruency effect: incongruent vs. congruent sentence endings						
48	4.05	-48	26	1	Inferior Frontal Gyrus	45
15	3.88	-53	10	19	Inferior Frontal Gyrus	44
48	3.74	-50	-43	8	Middle Temporal Gyrus	21
	3.62	-56	-32	2	Middle Temporal Gyrus	22
Congruency effect: congruent vs. incongruent sentence endings						
370	5.68	-33	-79	43	Precuneus	19
	4.28	-42	-56	50	Superior Parietal Lobule	7
	4.12	-53	-47	44	Inferior Parietal Lobule	40
1018	5.21	6	-27	35	Cingulate Gyrus	31
	5.15	-3	-27	35	Cingulate Gyrus	31
	4.79	-9	-59	47	Precuneus	7
207	4.76	48	-59	47	Inferior Parietal Lobule	40
	3.77	45	-68	37	Precuneus	39
	3.48	50	-41	46	Inferior Parietal Lobule	40
285	4.47	-24	28	40	Middle Frontal Gyrus	8
	4.42	-36	25	37	Precentral Gyrus	9
	3.99	-27	15	57	Middle Frontal Gyrus	6
213	4.31	21	34	45	Superior Frontal Gyrus	8
	4.26	27	29	48	Superior Frontal Gyrus	8
	4.09	24	43	37	Superior Frontal Gyrus	9
17	3.99	45	44	12	Middle Frontal Gyrus	10

Table 7.3. Results of voxel-based analysis for the sentence reading contrast across all children.

Cluster size	t	x	y	Z	Location	BA
Sentence reading: activation across the whole group						
728	9.71	-42	10	27	Inferior Frontal Gyrus	9
	6.74	-45	24	15	Inferior Frontal Gyrus	45
	6.62	-33	23	-4	Extra-Nuclear Gyrus	47
352	8.68	-42	-62	-12	Fusiform Gyrus	37
	6.31	-39	-45	-18	Fusiform Gyrus	37
	5.82	-33	-90	-3	Middle Occipital Gyrus	18
336	8.29	-6	20	46	Medial Frontal Gyrus	8
	5.46	9	17	46	Medial Frontal Gyrus	8
135	8.09	-24	-59	42	Superior Parietal Gyrus	7
140	7.45	33	26	-4	Inferior Frontal Gyrus	47
	5.40	39	24	10	Inferior Frontal Gyrus	13
184	7.17	-56	-32	2	Middle Temporal Gyrus	22
	5.61	-50	-43	13	Superior Temporal Gyrus	22
21	6.51	42	-59	-10	Fusiform Gyrus	37
55	6.45	48	-40	10	Middle Temporal Gyrus	21
17	5.99	39	-85	-3	Inferior Occipital Gyrus	18
Sentence reading: deactivation across the whole group						
1706	9.01	15	-76	-4	Lingual Gyrus	18
	8.73	12	-89	24	Cuneus	19
	7.64	-12	-89	24	Cuneus	19
65	7.33	-39	-74	34	Precuneus	19
63	6.95	-59	-30	37	Inferior Parietal Lobule	40
33	6.89	45	-74	29	Middle Temporal Gyrus	39
70	6.23	59	-24	43	Postcentral Gyrus	2
	5.56	59	-22	31	Postcentral Gyrus	2

Table 7.4. Results of the analyses for the anterior and posterior ROIs for the incongruency contrast.

ANOVA F(1,28)	ROI	Incongruency	Group	Incongruency * Group
CA vs. DYS	Anterior IPC	<1	1.29	19.74***
	Posterior IPC	1.42	<1	8.95**
RL vs. DYS	Anterior IPC	16.79***	4.47*	<1
	Posterior IPC	1.31	<1	<1
CA vs. RL	Anterior IPC	<1	1.72	10.93**
	Posterior IPC	5.53*	<1	8.95**

p-values ($^{+}$: p<0.1, *: p<0.05, **: p<0.01, ***: p<0.001)

Table 7.5. Results of the analyses for the inferior Parietal ROIs for the sentence reading contrast.

t-test t(1,28)	ROI	Sentence reading
CA vs. DYS	Superior IPC	4.21***
	Middle IPC	3.82***
	Inferior IPC	3.32**
RL vs. DYS	Superior IPC	1.99^{+}
	Middle IPC	3.13**
	Inferior IPC	2.42*
CA vs. RL	Superior IPC	-1<t<1
	Middle IPC	-1<t<1
	Inferior IPC	-1<t<1

p-values ($^{+}$: p<0.1, *: p<0.05, **: p<0.01, ***: p<0.001)

Table 7.6. Results of the latency and GFP analysis for the N400 effect and the P1, N1, P2 components.

Components sentence reading (t-values)						
t(1,28)	CA vs. RL		CA vs. DYS		RL vs. DYS	
	GFP	latency	GFP	latency	GFP	latency
P1	1.21	1.41	1.68	<1	<1	<1
N1	1.90^{+}	3.91***	<1	2.42*	1.90^{+}	2.39*
P2	<1	2.98**	<1	<1	<1	2.18*
N400 effect	<1	4.07***	<1	2.55*	1.01	<1

p-values ($^{+}$: p<0.1, *: p<0.05, **: p<0.01, ***: p<0.001)

Table 7.7. latency and GFP for P1, N1, P2 components an the N400 effect for each group

Component parameters (latency & amplitude)						
	CA		DYS		RL	
	latency	GFP	latency	GFP	latency	GFP
P1	134±19	3.90±2.01	129±22	3.00±1.17	126±11	3.28±1.00
N1	202±15	6.98±2.12	212±8	6.99±2.05	219±12	8.48±2.72
P2	333±16	3.81±1.28	338±15	3.88±1.60	348±14	3.99±1.64
N400 effect	398±60	3.84±1.11	508±178	3.93±1.44	537±137	3.53±0.93

8 General Discussion

The present work examined the deficient basic and semantic processing of dyslexic 5th grade children during sentence reading. By monitoring a semantic categorisation task in EEG and fMRI the spatiotemporal aspects of semantic processing and basic sentence reading could be described. We were able to distinguish the affected semantic processing from the more basic word processing deficits. In our second study we were able to verify that the semantic processing deficit is related to reduced reading abilities and is, hence, not specific for dyslexia.

8.1 Multimodal brain imaging

The application of a multimodal approach provided information regarding the temporal (EEG) as well as the spatial (fMRI) dimension in brain processing. The time course of the N400 component indicated different processing between incongruent and congruent sentence endings starting before 400 ms. Furthermore, semantic processing could be disentangled from more basic word recognition mechanisms indicated by prominent P1 and N1 components during word processing.

Similarly within fMRI, the influence of the basic sentence reading mechanisms could be experimentally controlled by a dichotomous semantic modulation of the sentence endings. Considering the entire 5th grade group this modulation was localised in the left hemispheric language network, mainly consisting of inferior frontal and temporal brain regions. Conversely, the basic sentence reading mechanisms were assessed by focussing on the processing of the entire sentences. Due to the inclusion of all stages of the reading process, e.g. phonological processing, a large bilateral language network across both hemispheres was activated.

To our knowledge, this is the first study to examine affected semantic processing in dyslexia in relation to basic sentence reading and word recognition mechanisms described by means of EEG and fMRI.

8.2 Semantic processing in dyslexia

The task design provided insight into the semantic processing of 5th grade dyslexic children in comparison to non-impaired 5th graders during sentence reading. Using EEG and fMRI in a semantic decision task, the children read simple four word sentences with endings that were meaningful (congruent) or not (incongruent). By contrasting these sentence endings the task is well suited to specifically investigate semantic processing. Hence, related to semantic modulation and not confounded with brain activity due to basic sentence reading and word recognition the semantic processing deficit in dyslexia could be assessed independently. Previous studies on word/sentence and semantic processing were confirmed.

Regarding the temporal dimension a modified N400 component of the EEG for dyslexic 5th grade readers was found. This is in line with previous neurophysiological research on semantic processing in dyslexia suggesting a reduced, topographically different or reduced N400 component (Brandeis et al., 1994; Helenius et al., 1999). In contrast, other studies did not find a semantic processing deficit, which can be explained by the different type of stimulus modality (Sabisch et al., 2006) used or by the younger age of the children, respectively (Neville et al., 1993; Silva-Pereyra et al., 2003). Further studies using slow presentation rates (Robichon et al., 2002; Silva-Pereyra et al., 2003) also failed to find affected semantic processing. These contradictory effects may depend on task requirements that propagate with increasing task difficulties, such as modality (presumably easier for the auditory modality) and increased presentation rates (presumably easier with slow presentation rates).

Conversely, basic word recognition mechanisms can be assessed by focussing on ERP components common to all words. On the one hand the P1 component occurring around 100ms is sensitive to physical stimulus characteristics such as stimulus size (Hauk and Pulvermuller, 2004; Khateb et al., 2002). On the other the N1 around 220 ms is sensitive to expertise (Brem et al., 2005) as it differentiates between words and word-like symbols after reading training (Maurer et al., 2007). In line with previous findings the present work revealed a topographically different P1 component for dyslexic children, suggesting a language independent basic visual perception impairment. The marginal delay of the N1 component may indicate a specific interfering effect on word processing.

The same methodological principle also holds for the spatial brain analysis in fMRI. In contrast to previous studies (Kronbichler et al., 2006; Meyler et al., 2007) in the present study specifically disentangled semantic processing from the more basic sentence reading mechanisms. While sentence reading - rather than semantic processing - includes additional stages of language processing (e.g. phonological decoding, print decoding) further brain regions (e.g. right hemispheric) were involved.

By controlling these confounding factors, the specific semantic deficit for dyslexics has been localised to inferior parietal brain regions. A previous fMRI study by (Booth et al., 2007) specifically examining semantic impairments in dyslexia by evaluating the relation between single words was confirmed.

Taken together, combined evidence of impaired semantic processing in dyslexic 5^{th} grade children was found. The spatio-temporal dimension was assessed by relating the semantic processing deficit to inferior parietal brain regions co-occurring with a reduction of the N400 effect. Furthermore the source localisation at 2 singular time points roughly confirmed the semantic effects across both methods but failed to causally relate the group differences obtained by fMRI to a certain time range in EEG. A possible explanation for the localisation failure may lie in the inability to detect the hemodynamic reductions in frontal brain regions due to small N400 variations. Furthermore, it is unclear whether the semantic impairments are specific for dyslexia or whether they can be explained by reduced reading abilities also occurring in younger children with fewer years of schooling.

8.3 Specificity of semantic processing in dyslexia

Hence, the second study was conducted to overcome the limitations of the first study and to facilitate the interpretation of the results. This was done by comparing both 5^{th} grade groups with an additional group of younger children matched to the reading abilities (absolute and relative) of both 5^{th} grade groups. The results of the first study were confirmed and emphasised the influence of reading ability on semantic processing on the one hand and rejected the assumption of a specific semantic impairment in dyslexia on the other. A uniform pattern across all modalities was found regarding EEG and fMRI data: no difference in the comparison between the 5^{th} grade dyslexics and the reading level matched younger control group and similar differences between these groups compared to the 5^{th} grade control group.

The EEG analysis revealed differences for the 5^{th} grade dyslexics as well for the younger control group compared to the 5^{th} grade control group within the N400 range. No difference was found between the two reading level matched groups, pointing to similar semantic processing in both groups. Confirming the results of the first study the analysis of the basic word recognition mechanisms revealed marginal P1 differences for the dyslexia group compared to both control groups. Thus, this effect is considered as specific for dyslexia and can not be attributed to differences in reading ability. Further differences were found within the N1 range between all experimental groups, suggesting dyslexia specific as well as developmental effects for the N1 component.

The same pattern of results was found in the fMRI analysis. As in the first study the dyslexic 5th graders showed the same reduced inferior parietal activity compared to the 5th grade controls. A similar effect was obtained by comparing the younger control group with the 5th grade controls. No incongruency effect difference was found between the dyslexic and the younger control group. Hence, similar to the results of the EEG analysis, the processing deficits were related to reading ability rather than specific for dyslexia. In contrast, the basic sentence reading mechanisms assessed by analysing the entire sentences showed a different pattern. There was no difference between the two control groups but a reduced frontal and inferior parietal activation for the dyslexic 5th graders compared to these groups. As the sentence reading contrast also included all processes of reading, including phonological processing, the sentence reading deficits may be partly related to phonological impairments. These findings were supported by Hoeft et al. using a similar reading level matched design.

8.4 Conclusions and outlook

The present work examined basic word processing and specific semantic processing deficits during sentence reading in dyslexia using multimodal imaging and a genuine developmental approach. Although basic visual, orthographic and phonological word processing deficits in dyslexia have already been studied with ERPs and fMRI in a variety of visual word processing task, this is the first study of children with dyslexia that uses multimodal functional imaging, and contrasts basic and semantic processing during sentence reading directly.

In a first part of the present work we found dyslexia related semantic impairments by revealing deviant processing in the temporal (a modified N400 component) as well as in the spatial (reduced activation of the inferior parietal cortex) domain. The 2nd part of the PhD thesis appraised the semantic deficit as unspecific for dyslexia and related the impairment to the lack of reading ability. Furthermore, dyslexia specific impairments have been shown for basic sentence reading and word recognition.

The main advantage of the present study design was that we were able to disentangle distinct influences and processes during language processing. In contrast, despite behavioural work has been shown that dyslexics exhibit a phonological deficit there's hardly any neuroimaging work that specifically investigates phonological processing (except for Maurer et al. (2007) for EEG and Temple et al, 2001 for fMRI). Due to assessing brain activity in comparison to an unspecific fixation baseline most studies were not able to exclude basic auditory and visual recognition processes which precede higher order language processing such as phonological processing.

The findings of the present PhD work related the deficit in dyslexics to posterior brain regions in response to semantic task requirements. However, it is unknown whether this functional deficit is related to a structural basis. Functional deviances are related to metabolic mechanisms revealed with fMRI. The structural deficit may be related to morphologic or connectivity changes.

These questions will be addressed in a further part of the whole dyslexia project is the assessment of connections between the cortical language areas and its relation to functional deviances in dyslexia. Further analyses are needed to clarify whether the finding of weaker fibre connections for poor adult readers in the arcuate fasciculus connecting the superior temporal cortex and the inferior frontal cortex. (Klingberg et al., 2000) can be replicated in the present sample.

For the present work on semantic processing, deficits in dyslexia were located in the inferior parietal cortex also involved in an interesting DTI study on reading in adults by Catani et al. (2005). The authors demonstrated the importance of that brain region for language processing by revealing a new, undescribed pathway. Bypassing the arcuate fasciculus it indirectly connects the superior temporal cortex (Wernicke´s area) with the inferior frontal cortex (Broca´s area) in two fibre bundles via the inferior parietal cortex. A closer look on these connections in the present child sample may shed some light on the function of the inferior parietal cortex within the language network as well as on semantic processing. Considering that we interpreted the developmentally related impairments in younger children and the reading impairment related problems of dyslexics as common endpoints of two distinct pathways, the connection between these 3 language regions might represent a concrete structural basis for this metaphoric pathway.

However, besides open questions regarding the strength of these pathways and their contribution to the function of the inferior parietal cortex, the semantic function of this parietal region itself is quite unclear. For example, Booth et al. (2007) found higher inferior parietal activity with increasing association strength for children. The present dichotomic design revealed the opposite pattern. Higher activation was found for incongruent (unrelated) than for congruent (highly related) stimuli. Hence, despite showing a deficit for dyslexic in both studies the contribution of the inferior parietal cortex to semantic variation remains unknown.

A similar uncertainty applies to the N400 component. This small and thus noise susceptible component shows inconsistent results across studies addressing semantic processing in dyslexia. A longer task with more stimuli, or one assessing the relation between single words similar to Rüsseler et al. (2007), as well as restricted filter settings might improve data quality. As typical, the N400 was not clearly visible in every subject, underlining the need for strong filtering. Fortunately, the application of a low pass filter of 5Hz lowered the N400 amplitude only marginally but substantially removed noise. However, due to the conflicting findings among ERP studies further work investigating the influence of presentation rate and age on dyslexic language processing are mandatory.

Taken together, further studies using connectivity models and tasks applying semantically varied stimuli are necessary to investigate the functional and structural role of the inferior parietal cortex as well as its contribution to dyslexia. Accounting for the problem of data quality a task with an increased amount of stimuli is well suited for investigation semantic processing.

As discussed above, these multimodal studies are the first to jointly investigate the spatiotemporal aspects of semantic processing and other aspects of sentence reading in dyslexia. In light of these findings a specific semantic processing deficit as well as a general developmental delayed in dyslexic children appears to be unlikely. Metaphorically speaking, the impairments of dyslexic children and younger controls in semantic processing can be described as a common endpoint preceded by two different pathways. The reduced reading abilities due to dyslexia lead to the same type of semantic impairments as the developmentally related reduced reading abilities in 2nd and 3rd graders do. Whereas the first pathway results from the deviance of an impaired language system the second pathway is due to the developmental effect of premature processing in younger children. The different course of these “pathways” was suggested by impairments in basic sentence reading and basic word recognition. A follow up measure of the younger control group and a comparison of that group with the present data would provide further evidence of the validity the findings. Further research on the role of the inferior parietal cortex in language processing in general and in specific semantic processing is mandatory to adequately describe the nature of that deficit in dyslexia.

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10 Curriculum Vitae

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Publications	Schulz E, Maurer U, van der Mark S, Bucher K, Brem S, Martin E, Brandeis D. 2008. Impaired semantic processing during sentence reading in children with dyslexia: combined fMRI and ERP evidence. NeuroImage. 41(1):153-168. Schulz E, Maurer U, van der Mark S, Bucher K, Brem S, Martin E, Brandeis D. (under review) . Reading for meaning in dyslexic and young children: EEG and fMRI evidence for distinct neural pathways but common endpoints.